(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 31 January 2002 (31.01.2002)

(10) International Publication Number WO 02/08288 A2

(51)	International Patent Classification7:		C07K 14/705	
(21)	International Ap	plication Number:	PCT/US01/2	1066
(22)	International Fili	ng Date: 29 June	2001 (29.06.2	2001)
(25)	Filing Language:		English	
(26)	Publication Language:		English	
(30)	Priority Data:			
(= -)	60/219,556	20 July 2000 (20.07.2000)	US
	60/220,585	25 July 2000 (US
	60/220,605	25 July 2000 (US
	60/220,607	25 July 2000 (US
	60/220,624	25 July 2000 ((25.07.2000)	US
	60/220,638	25 July 2000 (25.07.2000)	US
	60/220,664	25 July 2000 ((25.07.2000)	US
	60/220,666	25 July 2000 (US
	60/220,893	26 July 2000 (US
	PCT/US00/20710	28 July 2000 (US
	60/222,425	1 August 2000 (US
	60/227,133	22 August 2000 (US
	PCT/US00/23522	23 August 2000 (US
	PCT/US00/23328	24 August 2000 (US
	60/000,000	15 September 2000 ((15.09.2000)	US
	PCT/US00/30873			
		10 November 2000 (US
	60/253,646	28 November 2000 ((28.11.2000)	US
	PCT/US00/32678			
		1 December 2000 (US
	09/747,259	20 December 2000 ((20.12.2000)	US
	PCT/US00/34956	20 D 1 2000		US
	PCT/US01/06520	20 December 2000 ((20.12.2000)	US
	PC1/US01/00520	28 February 2001 ((26.02.2001)	US
	PCT/US01/06666	28 February 2001 (1 March 2001 (US
	09/816,744	22 March 2001 (US
	09/816,744	10 May 2001 (US
	09/854,208	10 May 2001 (US
	V21034,40U	10 May 2001 ((10.03.2001)	US

5 (72) Inventors; and

(75) Inventors/Applicants (for US only): BAKER, Kevin, P. [GB/US]; 14006 Indian Run Drive, Darnestown, MD 20878 (US). DESNOYERS, Luc [CA/US]; 2050 Stockton Street, San Francisco, CA 94133 (US), GERRITSEN, Mary, E. [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). GODOWSKI, Paul, J. [US/US]; 2627 Easton Drive. Burlingame, CA 94010 (US). GRIMALDI, J., Christopher [US/US]; 1434 36th Avenue, San Francisco, CA 94122 (US). GUR-NEV, Austin, L. [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). SMITH, Victoria [AU/US]; 19 Dwight Road, Burlingame, CA 94010 (US). STEPHAN, Jean-Philippe, F. [FR/US]; 320 C Lansdale Avenue, Millbrae, CA 94030 (US). WATANABE, Colin, K. [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). WOOD, William, I. [US/US]: 35 Southdown Court, Hillsborough, CA 94010

- (74) Agents: BARNES, Elizabeth, M. et al.: c/o GENEN-TECH, INC., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, 1E, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

 without international search report and to be republished upon receipt of that report

CA 94080-4990 (US).

25 May 2001 (25.05.2001) US

ning of each regular issue of the PCT Gazette.

(54) Title: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

(57) Abstract: The present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

02/08288

PCT/US01/17092

SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

FIELD OF THE INVENTION

The present invention relates generally to the identification and isolation of novel DNA and to the recombinant production of novel polypeptides.

5

10

15

20

25

30

BACKGROUND OF THE INVENTION

Extracellular proteins play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., <u>Proc. Natl. Acad. Sci.</u>, 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

Membrane-bound proteins and receptors can play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, surrival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptors.

Page 3 of 559

nerve growth factor receptor.

5

10

15

20

25

30

35

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interactions. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor or membrane-bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor or membrane-bound proteins.

SUMMARY OF THE INVENTION

In one embodiment, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93 % nucleic acid sequence identity, alternatively at least about 94 % nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at l

nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

5

10

15

20

25

30

35

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity alternatively at least about 95% nucleic acid sequence identity alternatively at least about 95% nucleic acid sequence identity alternatively at least about 95% nucleic acid sequence identity alternatively at least about 95% nucleic acid sequence identity alternatively at least about 95% nucleic acid sequence identity alternatively at least about 95% nucleic acid sequence identity

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 10 nucleotides in length, alternatively at least about 20 nucleotides in length, alternatively at least about 20 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 120 nucleotides in length, alternat

WC0208088 (IRe///E-AVOV208288 opc) Paga 5 ot 359

PCT/US01/21066

WO 02/08288

5

10

15

20

25

30

35

alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700 nucleotides in length. alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83%

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 80% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity and alternatively at least about 95% amino acid sequence identity at least about 95% amino acid sequence iden

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also horein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, E. coli, or yeast. A process for producing any of the herein described

WG0008068 (He ///E AVOVZ0623% opc)

Page 7 of 359

WO 02/08288 PCT/US01/21066

polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fe region of an immunoglobulin.

5

10

15

25

30

In another embodiment, the invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes which may be useful for isolating genomic and cDNA nucleotide sequences, measuring or detecting expression of an associated gene or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences. Preferred probe lengths are described above.

In yet other embodiments, the present invention is directed to methods of using the PRO polypeptides of the present invention for a variety of uses based upon the functional biological assay data presented in the Examples below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1B show a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO6004 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA92259".

20 Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figures 1A-1B.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence PRO4981 cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA94849-2960".

Figure 4 shows the amino acid sequence (SEQ ID NO:4) derived from the coding sequence of SEQ ID NO:3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO7174 cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA96883-2745".

Figure 6 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO5778 cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA96894-2675".

Figure 8 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) of a native sequence PRO4332 cDNA, wherein SEQ ID NO:9 is a clone designated herein as "DNA100272-2969".

Figure 10 shows the amino acid sequence (SEQ ID NO:10) derived from the coding sequence of SEQ ID NO:9 shown in Figure 9.

WC0208088 (IRe///E-AV-00208288 opc) Pege 8 of 359

WO 02/08288 PCT/US01/21066

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a native sequence PRO9799 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA108696-2966".

Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO9909 cDNA, wherein

5 SEQ ID NO:13 is a clone designated herein as "DNA117935-2801".

Figure 14 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence PRO9917 cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA119474-2803".

10 Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

Figure 17 shows a nucleotide sequence (SEQ ID NO:17) of a native sequence PRO9771 cDNA, wherein SEQ ID NO:17 is a clone designated herein as "DNA119498-2965".

Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ ID NO:17 shown in Figure 17.

15

25

30

ID NO:19 shown in Figure 19.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO9877 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA119502-2789".

Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ

20 Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO9903 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA119516-2797".

Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO9830 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA119530-2968".

Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence PRO7155 cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA121772-2741".

Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO9862 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA125148-2782".

Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ 35 ID NO:27 shown in Figure 27.

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO9882 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA125150-2793".

WC0208088 (IRe///E-AVOV208288 opc) Pege 9 ot 359

WO 02/08288 PCT/US01/21066

Figure 30 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID NO:29 shown in Figure 29.

Figure 31 shows a nucleotide sequence (SEQ ID NO:31) of a native sequence PRO9864 cDNA, wherein SEQ ID NO:31 is a clone designated herein as "DNA125151-2784".

Figure 32 shows the amino acid sequence (SEQ ID NO:32) derived from the coding sequence of SEQ 5 ID NO:31 shown in Figure 31.

Figure 33 shows a nucleotide sequence (SEQ ID NO:33) of a native sequence PRO10013 cDNA, wherein SEQ ID NO:33 is a clone designated herein as "DNA125181-2804".

Figure 34 shows the amino acid sequence (SEQ ID NO:34) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO9885 cDNA, wherein SEO ID NO:35 is a clone designated herein as "DNA125192-2794".

10

25

30

Figure 36 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

Figure 37 shows a nucleotide sequence (SEQ ID NO:37) of a native sequence PRO9879 cDNA, wherein SEO ID NO:37 is a clone designated herein as "DNA125196-2792".

Figure 38 shows the amino acid sequence (SEQ ID NO:38) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

Figure 39 shows a nucleotide sequence (SEQ ID NO:39) of a native sequence PRO10111 cDNA, wherein SEQ ID NO:39 is a clone designated herein as "DNA125200-2810".

20 Figure 40 shows the amino acid sequence (SEQ ID NO:40) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39.

Figure 41 shows a nucleotide sequence (SEQ ID NO:41) of a native sequence PRO9925 cDNA, wherein SEQ ID NO:41 is a clone designated herein as *DNA125214-2814*.

Figure 42 shows the amino acid sequence (SEQ ID NO:42) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

Figure 43 shows a nucleotide sequence (SEQ ID NO:43) of a native sequence PRO9905 cDNA, wherein SEQ ID NO:43 is a clone designated herein as "DNA125219-2799".

Figure 44 shows the amino acid sequence (SEQ ID NO:44) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) of a native sequence PRO10276 cDNA, wherein SEQ ID NO:45 is a clone designated herein as "DNA128309-2825".

Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a native sequence PRO9898 cDNA, wherein

SEQ ID NO:47 is a clone designated herein as "DNA129535-2796".

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

WC0208058 [Re///E-AVOC205288 opc] Page 10 of 550

WO 02/08288 PCT/US01/21066

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO9904 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA129549-2798".

Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO19632 cDNA, wherein

5 SEQ ID NO:51 is a clone designated herein as "DNA129580-2863".

Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a native sequence PRO19672 cDNA, wherein SEQ ID NO:53 is a clone designated herein as "DNA129794-2967".

10 Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a native sequence PRO9783 cDNA, wherein SEQ ID NO:55 is a clone designated herein as "DNA131590-2962".

Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ 15 ID NO:55 shown in Figure 55.

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a native sequence PRO10112 cDNA, wherein SEQ ID NO:57 is a clone designated herein as "DNA135173-2811".

Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

Figures 59A-59B show a nucleotide sequence (SEQ ID NO:59) of a native sequence PRO10284 cDNA, wherein SEQ ID NO:59 is a clone designated herein as "DNA138039-2828".

Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ ID NO:59 shown in Figures 59A-59B.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO10100 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA139540-2807".

25

Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figure 61.

Figure 63 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO19628 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "DNA139602-2859".

30 Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a native sequence PRO19684 cDNA, wherein SEQ ID NO:65 is a clone designated herein as "DNA139632-2880".

Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ 35 ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a native sequence PRO10274 cDNA, wherein SEQ ID NO:67 is a clone designated herein as "DNA139686-2823".

Page 11 of 359

WG0008068 [Re#/E/W/00206288 opc]

5

WO 02/08288 PCT/US01/21066

Figure 68 shows the amino acid sequence (SEQ ID NO:68) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a native sequence PRO9907 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA142392-2800".

Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a native sequence PRO9873 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA143076-2787".

Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO10201 cDNA, wherein SEO ID NO:73 is a clone designated herein as "DNA143294-2818".

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a native sequence PRO10200 cDNA, wherein

SEQ ID NO:75 is a clone designated herein as "DNA143514-2817".

Figure 76 shows the amino acid sequence (SEQ ID NO:76) derived from the coding sequence of SEQ

ID NO:75 shown in Figure 75.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a native sequence PRO10196 cDNA, wherein

SEQ ID NO:77 is a clone designated herein as "DNA144841-2816".

20 Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) of a native sequence PRO10282 cDNA, wherein SEQ ID NO:79 is a clone designated herein as "DNA148380-2827".

Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ 25 ID NO:79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) of a native sequence PRO19650 cDNA, wherein SEQ ID NO:81 is a clone designated herein as "DNA149995-2871".

Figure 82 shows the amino acid séquence (SEQ ID NO:82) derived from the coding sequence of SEQ ID NO:81 shown in Figure 81.

30 Figure 83 shows a nucleotide sequence (SEQ ID NO:83) of a native sequence PRO21184 cDNA, wherein SEQ ID NO:83 is a clone designated herein as "DNA167678:2963".

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID NO:83 shown in Figure 83.

Figure 85 shows a nucleotide sequence (SEQ ID NO:85) of a native sequence PRO21201 cDNA, wherein
35 SEQ ID NO:85 is a clone designated herein as "DNA168028-2956".

Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:85 shown in Figure 85.

Page 12 of 359

WCG268268 (IB#7/E-AVO6206236 opc.)

25

30

WO 02/08288 PCT/US01/21066

Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO21175 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA173894-2947".

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO21340 cDNA, wherein 5 SEQ ID NO:89 is a clone designated herein as "DNA176775-2957".

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO21384 cDNA, wherein SEO ID NO:91 is a clone designated herein as "DNA177313-2982".

Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO982 cDNA, wherein

SEQ ID NO:93 is a clone designated herein as "DNA57700-1408".

Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ

15 ID NO:93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence PRO1160 cDNA, wherein SEQ ID NO:95 is a clone designated herein as "DNA62872-1509".

Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

20 Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence PRO1187 cDNA, wherein SEO ID NO:97 is a clone designated herein as "DNA62876-1517".

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO1329 cDNA, wherein SEQ ID NO:99 is a clone designated herein as "DNA66660-1585".

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO231 cDNA, wherein SEQ ID NO:101 is a clone designated herein as "DNA34434-1139".

Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) of a native sequence PRO357 cDNA, wherein SEQ ID NO:103 is a clone designated herein as "DNA44804-1248".

Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ 35 ID NO:103 shown in Figure 103.

Figure 105 shows a nucleotide sequence (SEQ ID NO:105) of a native sequence PRO725 cDNA, wherein SEQ ID NO:105 is a clone designated herein as "DNA52758-1399".

WC0208058 [Re-WE-AVOC205288 opc] Page 13 of 550

WO 02/08288 PCT/US01/21066

Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

Figure 107 shows a nucleotide sequence (SEQ ID NO:107) of a native sequence PRO1155 cDNA, wherein SEQ ID NO:107 is a clone designated herein as "DNA59849-1504".

Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ ID NO:107 shown in Figure 107.

5

25

30

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) of a native sequence PRO1306 cDNA, wherein SEQ ID NO:109 is a clone designated herein as "DNA65410-1569".

Figure 110 shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:109 shown in Figure 109.

10 Figure 111 shows a nucleotide sequence (SEQ ID NO:111) of a native sequence PRO1419 cDNA, wherein SEO ID NO:111 is a clone designated herein as "DNA71290-1630".

Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:111 shown in Figure 111.

Figure 113 shows a nucleotide sequence (SEQ ID NO:113) of a native sequence PRO229 cDNA, wherein
15 SEQ ID NO:113 is a clone designated herein as "DNA33100-1159".

Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figure 113.

Figure 115 shows a nucleotide sequence (SEQ ID NO:115) of a native sequence PRO1272 cDNA, wherein SEQ ID NO:115 is a clone designated herein as "DNA64896-1539".

20 Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:115 shown in Figure 115.

Figure 117 shows a nucleotide sequence (SEQ ID NO:117) of a native sequence PRO4405 cDNA, wherein SEQ ID NO:117 is a clone designated herein as "DNA84920-2614".

Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:117 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO:119) of a native sequence PRO181 cDNA, wherein SEQ ID NO:119 is a clone designated herein as "DNA23330-1390".

Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:119 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:121) of a native sequence PRO214 cDNA, wherein SEQ ID NO:121 is a clone designated herein as "DNA32286-1191".

Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:121 shown in Figure 121.

Figure 123 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO247 cDNA, wherein 35 SEQ ID NO:123 is a clone designated herein as "DNA35673-1201".

Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 123.

Page 14 of 359

WC6268888 (IBH //E-AVO6268288 opc)

10

15

20

30

WO 02/08288 PCT/US01/21066

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) of a native sequence PRO337 cDNA, wherein SEQ ID NO:125 is a clone designated herein as "DNA43316-1237".

Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

Figure 127 shows a nucleotide sequence (SEQ ID NO:127) of a native sequence PRO526 cDNA, wherein

5 SEQ ID NO:127 is a clone designated herein as "DNA44184-1319".

Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) of a native sequence PRO363 cDNA, wherein SEQ ID NO:129 is a clone designated herein as "DNA45419-1252".

Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

Figure 131 shows a nucleotide sequence (SEQID NO:131) of a native sequence PRO531 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "DNA48314-1320".

Figure 132 shows the amino acid sequence (SEQ ID NO: 132) derived from the coding sequence of SEQ ID NO: 131 shown in Figure 131.

Figure 133 shows a nucleotide sequence (SEQ ID NO:133) of a native sequence PRO1083 cDNA,

wherein SEQ ID NO:133 is a clone designated herein as "DNA50921-1458".

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ

ID NO:133 shown in Figure 133.

Figure 135 shows a nucleotide sequence (SEQ ID NO:135) of a native sequence PRO840 cDNA, wherein SEQ ID NO:135 is a clone designated herein as "DNA53987".

Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

Figure 137 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO1080 cDNA,

wherein SEQ ID NO:137 is a clone designated herein as "DNA56047-1456".

Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) of a native sequence PRO788 cDNA, wherein SEQ ID NO:139 is a clone designated herein as "DNA56405-1357".

Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

Figure 141 shows a nucleotide sequence (SEQ ID NO:141) of a native sequence PRO1478 cDNA, wherein SEQ ID NO:141 is a clone designated herein as "DNA56531-1648".

Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ 35 ID NO:141 shown in Figure 141.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) of a native sequence PRO1134 cDNA, wherein SEQ ID NO:143 is a clone designated herein as "DNA56865-1491".

WC0208088 [IRe///E-AVOV208288 opc] Page 15 of 355

WO 02/08288 PCT/US01/21066

Figure 144 shows the amino acid sequence (SEQ ID NO:144) derived from the coding sequence of SEQ ID NO:143 shown in Figure 143.

Figure 145 shows a nucleotide sequence (SEQ ID NO:145) of a native sequence PRO826 cDNA, wherein SEQ ID NO:145 is a clone designated herein as "DNA57694-1341".

Figure 146 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:145 shown in Figure 145.

5

10

20

25

30

35

Figure 147 shows a nucleotide sequence (SEQ ID NO:147) of a native sequence PRO1005 cDNA, wherein SEQ ID NO:147 is a clone designated herein as "DNA57708-1411".

Figure 148 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:147 shown in Figure 147.

Figure 149 shows a nucleotide sequence (SEQ ID NO:149) of a native sequence PRO809 cDNA, wherein SEQ ID NO:149 is a clone designated herein as "DNA57836-1338".

Figure 150 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:149 shown in Figure 149.

Figure 151 shows a nucleotide sequence (SEQ ID NO:151) of a native sequence PRO1194 cDNA,

15 wherein SEQ ID NO:151 is a clone designated herein as "DNA57841-1522".

Figure 152 shows the amino acid sequence (SEQ ID NO:152) derived from the coding sequence of SEQ ID NO:151 shown in Figure 151.

Figure 153 shows a nucleotide sequence (SEQ ID NO:153) of a native sequence PRO1071 cDNA, wherein SEQ ID NO:153 is a clone designated herein as "DNA58847-1383".

Figure 154 shows the amino acid sequence (SEQ ID NO:154) derived from the coding sequence of SEQ ID NO:153 shown in Figure 153.

Figure 155 shows a nucleotide sequence (SEQ ID NO:155) of a native sequence PRO1411 cDNA, wherein SEQ ID NO:155 is a clone designated herein as "DNA59212-1627".

Figure 156 shows the amino acid sequence (SEQ ID NO:156) derived from the coding sequence of SEQ ID NO:155 shown in Figure 155.

Figure 157 shows a nucleotide sequence (SEQ ID NO:157) of a native sequence PRO1309 cDNA, wherein SEQ ID NO:157 is a clone designated herein as "DNA59588-1571".

Figure 158 shows the amino acid sequence (SEQ ID NO:158) derived from the coding sequence of SEQ ID NO:157 shown in Figure 157.

Figure 159 shows a nucleotide sequence (SEQ ID NO:159) of a native sequence PRO1025 cDNA, wherein SEQ ID NO:159 is a clone designated herein as "DNA59622-1334".

Figure 160 shows the amino acid sequence (SEQ ID NO:160) derived from the coding sequence of SEQ ID NO:159 shown in Figure 159.

Figure 161 shows a nucleotide sequence (SEQ ID NO:161) of a native sequence PRO1181 cDNA, wherein SEQ ID NO:161 is a clone designated herein as "DNA59847-2510".

Figure 162 shows the amino acid sequence (SEQ ID NO:162) derived from the coding sequence of SEQ ID NO:161 shown in Figure 161.

WCocoloosa (iller/IIIE AN Orizoscate opc.)
Pager 14 on 556

WO 02/08288 PCT/US01/21066

Figure 163 shows a nucleotide sequence (SEQ ID NO:163) of a native sequence PRO1126 cDNA, wherein SEO ID NO:163 is a clone designated herein as "DNA60615-1483".

Figure 164 shows the amino acid sequence (SEQ ID NO:164) derived from the coding sequence of SEQ ID NO:163 shown in Figure 163.

Figure 165 shows a nucleotide sequence (SPQ ID NO:165) of a native sequence PRO1186 cDNA,

5 wherein SEQ ID NO:165 is a clone designated herein as "DNA60621-1516".

Figure 166 shows the amino acid sequence (SEQ ID NO:166) derived from the coding sequence of SEQ ID NO:165 shown in Figure 165.

Figure 167 shows a nucleotide sequence (SEQ ID NO:167) of a native sequence PRO1192 cDNA, wherein SEQ ID NO:167 is a clone designated herein as "DNA62814-1521".

Figure 168 shows the amino acid sequence (SEQ ID NO:168) derived from the coding sequence of SEQ ID NO:167 shown in Figure 167.

10

15

25

30

35

Figure 169 shows a nucleotide sequence (SEQ ID NO:169) of a native sequence PRO1244 cDNA, wherein SEQ ID NO:169 is a clone designated herein as "DNA64883-1526".

Figure 170 shows the amino acid sequence (SEQ ID NO:170) derived from the coding sequence of SEQ ID NO:169 shown in Figure 169.

Figure 171 shows a nucleotide sequence (SEQ ID NO:171) of a native sequence PRO1274 cDNA, wherein SEQ ID NO:171 is a clone designated herein as "DNA64889-1541".

Figure 172 shows the amino acid sequence (SEQ ID NO:172) derived from the coding sequence of SEQ ID NO:171 shown in Figure 171.

20 Figure 173 shows a nucleotide sequence (SEQ ID NO:173) of a native sequence PRO1412 cDNA, wherein SEQ ID NO:173 is a clone designated herein as "DNA64897-1628".

Figure 174 shows the amino acid sequence (SEQ ID NO:174) derived from the coding sequence of SEQ ID NO:173 shown in Figure 173.

Figure 175 shows a nucleotide sequence (SEQ ID NO:175) of a native sequence PRO1286 cDNA, wherein SEO ID NO:175 is a clone designated herein as "DNA64903-1553".

Figure 176 shows the amino acid sequence (SEQ ID NO:176) derived from the coding sequence of SEQ ID NO:175 shown in Figure 175.

Figure 177 shows a nucleotide sequence (SEQ ID NO:177) of a native sequence PRO1330 cDNA, wherein SEO ID NO:177 is a clone designated herein as "DNA64907-1163-1".

Figure 178 shows the amino acid sequence (SEQ ID NO:178) derived from the coding sequence of SEQ ID NO:177 shown in Figure 177.

Figure 179 shows a nucleotide sequence (SEQ ID NO:179) of a native sequence PRO1347 cDNA, wherein SEQ ID NO:179 is a clone designated herein as "DNA64950-1590".

Figure 180 shows the amino acid sequence (SEQ ID NO:180) derived from the coding sequence of SEQ ID NO:179 shown in Figure 179.

Figure 181 shows a nucleotide sequence (SEQ ID NO:181) of a native sequence PRO1305 cDNA, wherein SEQ ID NO:181 is a clone designated herein as "DNA64952-1568".

WC0208058 [Re-WE-AVOC205288 opc] Page 17 of 556

WO 02/08288 PCT/US01/21066

Figure 182 shows the amino acid sequence (SEQ ID NO:182) derived from the coding sequence of SEQ ID NO:181 shown in Figure 181.

Figure 183 shows a nucleotide sequence (SEQ ID NO:183) of a native sequence PRO1273 cDNA, wherein SEQ ID NO:183 is a clone designated herein as "DNA65402-1540".

Figure 184 shows the amino acid sequence (SEQ ID NO:184) derived from the coding sequence of SEQ 5 ID NO:183 shown in Figure 183.

Figure 185 shows a nucleotide sequence (SBQ ID NO:185) of a native sequence PRO1279 cDNA, wherein SBQ ID NO:185 is a clone designated herein as "DNA65405-1547".

Figure 186 shows the amino acid sequence (SEQ ID NO:186) derived from the coding sequence of SEQ ID NO:185 shown in Figure 185.

10 Figure 187 shows a nucleotide sequence (SEQ ID NO:187) of a native sequence PRO1340 cDNA, wherein SEO ID NO:187 is a clone designated herein as "DNA66663-1598".

Figure 188 shows the amino acid sequence (SEQ ID NO:188) derived from the coding sequence of SEQ ID NO:187 shown in Figure 187.

Figure 189 shows a nucleotide sequence (SEQ ID NO:189) of a native sequence PRO1338 cDNA,

15 wherein SEO ID NO:189 is a clone designated herein as "DNA66667".

Figure 190 shows the amino acid sequence (SEQ ID NO:190) derived from the coding sequence of SEQ ID NO:189 shown in Figure 189.

Figure 191 shows a nucleotide sequence (SEQ ID NO:191) of a native sequence PRO1343 cDNA, wherein SEQ ID NO:191 is a clone designated herein as "DNA66675-1587".

20 Figure 192 shows the amino acid sequence (SEQ ID NO:192) derived from the coding sequence of SEQ ID NO:191 shown in Figure 191.

Figure 193 shows a nucleotide sequence (SEQ ID NO:193) of a native sequence PRO1376 cDNA, wherein SEQ ID NO:193 is a clone designated herein as "DNA67300-1605".

Figure 194 shows the amino acid sequence (SEQ ID NO:194) derived from the coding sequence of SEQ ID NO:193 shown in Figure 193.

Figure 195 shows a nucleotide sequence (SEQ ID NO:195) of a native sequence PRO1387 cDNA, wherein SEQ ID NO:195 is a clone designated herein as "DNA68872-1620".

25

30

Figure 196 shows the amino acid sequence (SEQ ID NO:196) derived from the coding sequence of SEQ ID NO:195 shown in Figure 195.

Figure 197 shows a nucleotide sequence (SEQ ID NO:197) of a native sequence PRO1409 cDNA, wherein SEQ ID NO:197 is a clone designated herein as "DNA71269-1621".

Figure 198 shows the amino acid sequence (SEQ ID NO:198) derived from the coding sequence of SEQ ID NO:197 shown in Figure 197.

Figure 199 shows a nucleotide sequence (SBQ ID NO:199) of a native sequence PRO1488 cDNA,

35 wherein SEQ ID NO:199 is a clone designated herein as *DNA73736-1657*.

Figure 200 shows the amino acid sequence (SEQ ID NO:200) derived from the coding sequence of SEQ ID NO:199 shown in Figure 199.

Page 18 of 359

PCT/US01/21066

Figure 201 shows a nucleotide sequence (SEQ ID NO:201) of a native sequence PRO1474 cDNA,

WC6268888 (IBH //E-AVO6268288 opc)

30

WO 02/08288

wherein SEQ ID NO:201 is a clone designated herein as "DNA73739-1645".

Figure 202 shows the amino acid sequence (SEQ ID NO:202) derived from the coding sequence of SEQ ID NO:201 shown in Figure 201.

Figure 203 shows a nucleotide sequence (SEQ ID NO:203) of a native sequence PRO1917 cDNA,

5 wherein SEQ ID NO:203 is a clone designated herein as "DNA76400-2528".

Figure 204 shows the amino acid sequence (SEQ ID NO: 204) derived from the coding sequence of SEQ ID NO: 203 shown in Figure 203.

Figure 205 shows a nucleotide sequence (SEQ ID NO:205) of a native sequence PRO1760 cDNA, wherein SEQ ID NO:205 is a clone designated herein as "DNA76532-1702".

10 Figure 206 shows the amino acid sequence (SEQ ID NO:206) derived from the coding sequence of SEQ ID NO:205 shown in Figure 205.

Figure 207 shows a nucleotide sequence (SEQ ID NO:207) of a native sequence PRO1567 cDNA, wherein SEQ ID NO:207 is a clone designated herein as "DNA76541-1675".

Figure 208 shows the amino acid sequence (SEQ ID NO:208) derived from the coding sequence of SEQ 15 ID NO:207 shown in Figure 207.

Figure 209 shows a nucleotide sequence (SEQ ID NO:209) of a native sequence PRO1887 cDNA, wherein SEQ ID NO:209 is a clone designated herein as "DNA79862-2522".

Figure 210 shows the amino acid sequence (SEQ ID NO:210) derived from the coding sequence of SEQ ID NO:209 shown in Figure 209.

20 Figure 211 shows a nucleotide sequence (SEQ ID NO:211) of a native sequence PRO1928 cDNA, wherein SEO ID NO:211 is a clone designated herein as "DNA81754-2532".

Figure 212 shows the amino acid sequence (SEQ ID NO:212) derived from the coding sequence of SEQ ID NO:211 shown in Figure 211.

Figure 213 shows a nucleotide sequence (SEQ ID NO:213) of a native sequence PRO4341 cDNA,

25 wherein SEQ ID NO:213 is a clone designated herein as "DNA81761-2583".

Figure 214 shows the amino acid sequence (SEQ ID NO:214) derived from the coding sequence of SEQ ID NO:213 shown in Figure 213.

Figure 215 shows a nucleotide sequence (SEQ ID NO:215) of a native sequence PRO5723 cDNA, wherein SEO ID NO:215 is a clone designated herein as "DNA82361".

Figure 216 shows the amino acid sequence (SEQ ID NO:216) derived from the coding sequence of SEQ ID NO:215 shown in Figure 215.

Figure 217 shows a nucleotide sequence (SEQ IID NO:217) of a native sequence PRO1801 cDNA, wherein SEQ ID NO:217 is a clone designated herein as "DNA83500-2506".

Figure 218 shows the amino acid sequence (SEQ ID NO:218) derived from the coding sequence of SEQ 35 ID NO:217 shown in Figure 217.

Figure 219 shows a nucleotide sequence (SEQ ID NO:219) of a native sequence PRO4333 cDNA, wherein SEO ID NO:219 is a clone designated herein as "DNA84210-2576".

WC0208358 [Re///E-AVOC205238 opc] Page 10 of 550

WO 02/08288 PCT/US01/21066

Figure 220 shows the amino acid sequence (SEQ ID NO:220) derived from the coding sequence of SEQ ID NO:219 shown in Figure 219.

Figure 221 shows a nucleotide sequence (SEQ ID NO:221) of a native sequence PRO3543 cDNA, wherein SEQ ID NO:221 is a clone designated herein as "DNA86571-2551".

Figure 222 shows the amino acid sequence (SEQ ID NO:222) derived from the coding sequence of SEQ 5 ID NO:221 shown in Figure 221.

Figure 223 shows a nucleotide sequence (SEQ ID NO:223) of a native sequence PRO3444 cDNA, wherein SEO ID NO:223 is a clone designated herein as "DNA87997".

Figure 224 shows the amino acid sequence (SEQ ID NO:224) derived from the coding sequence of SEQ ID NO:223 shown in Figure 223.

Figure 225 shows a nucleotide sequence (SEQ ID NO:225) of a native sequence PRO4302 cDNA, wherein SEQ ID NO:225 is a clone designated herein as "DNA92218-2554".

Figure 226 shows the amino acid sequence (SEQ ID NO:226) derived from the coding sequence of SEQ ID NO:225 shown in Figure 225.

Figure 227 shows a nucleotide sequence (SEQ ID NO:227) of a native sequence PRO4322 cDNA,

wherein SEQ ID NO:227 is a clone designated herein as "DNA92223-2567".

Figure 228 shows the amino acid sequence (SEQ ID NO:228) derived from the coding sequence of SEQ ID NO:227 shown in Figure 227.

Figure 229 shows a nucleotide sequence (SEQ ID NO:229) of a native sequence PRO5725 cDNA, wherein SEO ID NO:229 is a clone designated herein as "DNA92265-2669".

Figure 230 shows the amino acid sequence (SEQ ID NO:230) derived from the coding sequence of SEQ ID NO:229 shown in Figure 229.

20

25

30

35

Figure 231 shows a nucleotide sequence (SEQ ID NO:231) of a native sequence PRO4408 cDNA, wherein SEQ ID NO:231 is a clone designated herein as "DNA92274-2617".

Figure 232 shows the amino acid sequence (SEQ ID NO:232) derived from the coding sequence of SEQ ID NO:231 shown in Figure 231.

Figure 233 shows a nucleotide sequence (SEQ ID NO:233) of a native sequence PRO9940 cDNA, wherein SEQ ID NO:223 is a clone designated herein as "DNA92282".

Figure 234 shows the amino acid sequence (SEQ ID NO:234) derived from the coding sequence of SEQ ID NO:233 shown in Figure 233.

Figure 235 shows a nucleotide sequence (SEQ ID NO:235) of a native sequence PRO7154 cDNA, wherein SEQ ID NO:235 is a clone designated herein as "DNA108760-2740".

Figure 236 shows the amino acid sequence (SEQ ID NO:236) derived from the coding sequence of SEQ ID NO:235 shown in Figure 235.

Figure 237 shows a nucleotide sequence (SEQ ID NO:237) of a native sequence PRO7425 cDNA, wherein SEQ ID NO:237 is a clone designated herein as "DNA108792-2753".

Figure 238 shows the amino acid sequence (SEQ ID NO:238) derived from the coding sequence of SEQ ID NO:237 shown in Figure 237.

Page 20 of 359

WO 02/08288 PCT/US01/21066

Figure 239 shows a nucleotide sequence (SEQ ID NO:239) of a native sequence PRO6079 cDNA, wherein SEQ ID NO:239 is a clone designated herein as "DNA111750-2706".

Figure 240 shows the amino acid sequence (SEQ ID NO:240) derived from the coding sequence of SEQ ID NO:239 shown in Figure 239.

Figure 241 shows a nucleotide sequence (SEQ ID NO:241) of a native sequence PRO9836 cDNA, wherein SEQ ID NO:241 is a clone designated herein as "DNA119514-2772".

Figure 242 shows the amino acid sequence (SEQ ID NO:242) derived from the coding sequence of SEQ ID NO:241 shown in Figure 241.

Figure 243 shows a nucleotide sequence (SEQ ID NO:243) of a native sequence PRO10096 cDNA, wherein SEQ ID NO:243 is a clone designated herein as "DNA125185-2806".

Figure 244 shows the amino acid sequence (SEQ ID NO:244) derived from the coding sequence of SEQ ID NO:243 shown in Figure 243.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. <u>Definitions</u>

WCG268888 (IBH // E-AVO6206288 opc)

5

10

15

20

25

30

35

The terms "PRO polypeptides" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide and "PRO/number" is provided as an actual numerical designation as used herein enonpass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptide described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptide disclosed herein.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues designated herein as amino acid position 1 in the figures, it

WO 02/08288 PCT/US01/21066

acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain way vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are comtemplated by the present invention.

5

10

15

20

25

30

35

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., <u>Prot. Eng.</u> 10:1-6 (1997) and von Heinje et al., <u>Nucl. Acids. Res.</u> 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alt

10

15

20

25

30

WO 02/08288 PCT/US01/21066

sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence acking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 100 amino

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Mcgalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence B is calculated as follows:

35

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALJGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" represents the amino acid sequence of a phypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X, "Y" and "Z" each represent different hypothetical amino acid residues.

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % amino acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Favymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an the amino acid sequence A is the comparison amino acid sequence identity to the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence B (which can alternatively be phrased as a given amino acid sequence B) is calculated as follows:

WC0208088 [Re///E-AVOV206288 opc] Page 38 of 356

PCT/US01/21066

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

WO 02/08288

5

10

15

20

25

30

35

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96 % nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99 % nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 500 nucleotides in length, al

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alienment for purposes of determining percent

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % mucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXUS10087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D is calculated as follows:

100 times the fraction W/Z

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "PRO-DNA" to the nucleic acid sequence designated "PRO-DNA" to the nucleic acid sequence of interest, "Comparison DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides.

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % nucleic acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i.e., the sequence egainst

10

15

WO 02/08288 PCT/US01/21066

which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polymelcotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement *an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B*, the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoft for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D is calculated as follows:

100 times the fraction W/Z

20

30

35

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

25 In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides

may be those that are encoded by a PRO variant polynucleotide.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDs-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide in situ within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be present. Ordinarily, however, isolated

Page 27 of 359

WO 02/08288 PCT/US01/21066

polypeptide will be prepared by at least one purification step.

WC6268268 [IBe://E-AV06206236 opc.]

5

10

15

20

25

30

35

An "isolated" PRO polypeptide-encoding mucleic acid or other polypeptide-encoding mucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecules is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polyopeptide if it is expressed as a preprotein that participates in the secretion of the polyopeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody compositions with polyepitopic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology. Wiley Interescience Publishers. (1995).

15

20

25

30

35

WO 02/08288 PCT/US01/21066

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride(0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 $\mu g/ml$), 0.1% SDS, and 10% dextran sulfate at 42°C; with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., <u>Molecular Cloning:</u>
<u>A Laboratory Manual</u>, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent that those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Deahardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a 'tag polypeptide'. The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues an usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as 1sG-1, 1sG-2, 1sG-3, or 1sG-4 subtypes, 1sA (including 1sA-1 and 1sA-2), 1sE, 1sD or 1sM.

"Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

WC0208088 [Re-WE-AV-04208288 opc] Page 20 of 356

PCT/US01/21066

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist artibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

WO 02/08288

5

10

15

20

25

30

35

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is evelic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpytrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitot; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEENTM, polyethylene glycol (PEG), and PLIRONICSYM.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab'), and Fv fragments; diabodies; linear antibodies (Zapata et al., <u>Protein Eng.</u> 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab'), fragment that has two antigen-combining sites and is still

capable of cross-linking antigen.

5

10

15

20

25

30

35

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_{II}-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH1 is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthum in <u>The Pharmacology of Monoclonal Antibodies</u>, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_{ij}) connected to a light-chain variable domain (V_{ij}) in the same polypeptide chain $(V_{ir}V_{ij})$. By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6444 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodinents, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing

10

15

20

WO 02/08288 PCT/US01/21066

conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the autibody's natural environment will not be present.

Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word "tabe!" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4.275.149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly airanged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

An "effective amount" of a polypeptide disclosed herein or an agonist or antagonist thereof is an amount sufficient to carry out a specifically stated purpose. An "effective amount" may be determined empirically and in a routine manner, in relation to the stated nurpose.

50

55

WO 02/08288

PCT/US01/21066

Table 1

```
/*
         * C-C increased from 12 to 15
         * Z is average of EO
 5
         * B is average of ND
         * match with stop is M; stop-stop = 0; J (joker) match = 0
        #define M
                        -8
                                 /* value of a match with a stop */
10
                 dav[26][26] = {
              ABCDEFGHIJKLMNOPQRSTUVWXYZ*/
        /* A */
                  { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
        /* B */
                  { 0, 3, 4, 3, 2, 5, 0, 1, 2, 0, 0, 3, 2, 2, M, 1, 1, 0, 0, 0, 0, 2, 5, 0, 3, 1},
        /* C */
                  {-2,-4,15,-5,-5,-4,-3,-3,-2, 0,-5,-6,-5,-4, M,-3,-5,-4, 0,-2, 0,-2,-8, 0, 0,-5},
15
        /* D */
                  { 0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2, M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2},
        /* E */
                  { 0, 2,-5, 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 1, M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 3},
                  /* F */
        /* G */
        /* H */
20
        /* I */
                  {-1,-2,-2,-2,-1,-3,-2, 5, 0,-2, 2, 2,-2, M,-2,-2,-1, 0, 0, 4,-5, 0,-1,-2},
        /* J */
                  /* K */
                  {-1, 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1, M,-1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0},
        /* L */
                  {-2,-3,-6,-4,-3, 2,-4,-2, 2, 0,-3, 6, 4,-3,_M,-3,-2,-3,-3,-1, 0, 2,-2, 0,-1,-2},
        /* M */
                  {-1,-2,-5,-3,-2, 0,-3,-2, 2, 0, 0, 4, 6,-2, M,-2,-1, 0,-2,-1, 0, 2,-4, 0,-2,-1},
2.5
        /* N */
                  /* O */
       /* P */
                  {1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1, M, 6, 0, 0, 1, 0, 0,-1,-6, 0,-5, 0}, {0, 1,-5, 2, 2,-5,-1, 3,-2, 0, 1,-2,-1, 1, M, 0, 4, 1,-1,-1, 0,-2,-5, 0,-4, 3}, {-2, 0,-4,-1,-1,-4,-3, 2,-2, 0, 3,-3, 0, M, 0, 1, 6, 0,-1, 0,-2, 2, 0,-4, 0},
       /* Q */
       /* R */
30
        /* S */
                  { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
        /* T */
                  { 1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0,-1,-1, 0, M, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0},
        /* U */
                  /* V */
       /* W */
35
       /* X */
       /* Y */
       /* Z */
                  { 0, 1,-5, 2, 3,-5, 0, 2,-2, 0, 0,-2,-1, 1, M, 0, 3, 0, 0, 0, 0, 0,-2,-6, 0,-4, 4}
       };
40
```

PCT/US01/21066

WO 02/08288

Table 1 (cont')

```
10
         #include < stdio.h>
         #include < ctype.h>
  5
         #define MAXJMP
                                              /* max jumps in a diag */
                                               /* don't continue to penalize gaps larger than this */
         #define MAXGAP
                                     24
         #define JMPS
                                     1024
                                               /* max jmps in an path */
         #define MX
                                     4
                                              /* save if there's at least MX-1 bases since last jmp */
10
         #define DMAT
                                     3
                                               /* value of matching bases */
         #define DMIS
                                     0
                                               /* penalty for mismatched bases */
         #define DINSO
                                              /* penalty for a gap */
                                     8
         #define DINS1
                                              /* penalty pcr base */
                                     1
15
                                              /* penalty for a gap */
         #define PINSO
                                     8
         #define PINS1
                                     4
                                              /* penalty per residue */
         struct jmp {
                                     n[MAXJMP]:
                                                        /* size of jmp (neg for dely) */
20
                                     x[MAXJMP];
                                                        /* base no. of imp in seq x */
                  unsigned short
         }:
                                                        /* limits seq to 2^16 -1 */
         struct diag {
                                                        /* score at last jmp */
                  int
                                     score;
25
                  long
                                     offset:
                                                        /* offset of prev block */
                  short
                                     iimp:
                                                        /* current jmp index */
                                                        /* list of imps */
                  struct imp
                                     ip;
        };
30
         struct path {
                  int
                                              /* number of leading spaces */
                  short
                            n[JMPS]; /* size of jmp (gap) */
                            x[JMPS]; /* loc of jmp (last elem before gap) */
        };
35 -
                            *ofile;
        char
                                                        /* output file name */
                            *namex[2];
        char
                                                        /* seq names: getseqs() */
         char
                            *prog:
                                                        /* prog name for err msgs */
         char
                            *seqx[2];
                                                        /* seqs: getseqs() */
40
                           dmax;
        int
                                                        /* best diag: nw() */
         int
                            dmax0;
                                                        /* final diag */
        int
                            dna;
                                                        /* set if dna: main() */
        int
                            endgaps;
                                                        /* set if penalizing end gaps */
        int
                                                        /* total gaps in seqs */
                            gapx, gapy;
45
         int
                           len0, len1;
                                                        /* seg lens */
        int
                            ngapx, ngapy;
                                                        /* total size of gaps */
        int
                                                        /* max score: nw() */
                            smax;
        ínt
                            *xbm;
                                                        /* bitmap for matching */
        long
                            offset:
                                                        /* current offset in imp file */
50
         struct
                  diag
                            *dx:
                                                        /* holds diagonals */
                                                       /* holds path for segs */
        struct
                  path
                           pp[2];
        char
                            *calloc(), *malloc(), *index(), *strcpy();
        char
                            *getseq(), *g calloc();
55
```

WO 02/08288

PCT/US01/21066

Table 1 (cont')

```
/* Needleman-Wunsch alignment program
         * usage: progs file1 file2
         * where file1 and file2 are two dna or two protein sequences.
 5
         * The sequences can be in upper- or lower-case an may contain ambiguity
         * Any lines beginning with ';', '>' or '<' are ignored
          * Max file length is 65535 (limited by unsigned short x in the jmp struct)
           A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
            Output is in the file "align.out"
10
         * The program may create a tmp file in /tmp to hold info about traceback.
         * Original version developed under BSD 4.3 on a vax 8650
         #include "nw.h"
15
        #include "day.h"
        static
                   dbval[26] = {
                  1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
        }:
20
        static
                  pbval[26] = {
                  1, 2|(1 < <('D'-'A'))|(1 < <('N'-'A')), 4, 8, 16, 32, 64,
                  128, 256, 0xFFFFFFF, 1 < < 10, 1 < < 11, 1 < < 12, 1 < < 13, 1 < < 14,
                  1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
25
                  1< <23, 1< <24, 1< <25 | (1< <('E'-'A')) | (1< <('Q'-'A'))
        3:
        main(ac, av)
                                                                                                                        main
                  int
                           ac:
30
                  char
                           *av[];
        {
                  prog = av[0];
                  if (ac != 3) {
                           fprintf(stderr, "usage: %s file1 file2\n", prog);
35
                           fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
                           fprintf(stderr, "The sequences can be in upper- or lower-case\n");
                           fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
                           forintf(stderr, "Output is in the file \"align.out\"\n"):
                           exit(1):
40
                  namex[0] = av[1];
                  namex[1] = av[2];
                  segx[0] = getseg(namex[0], &len0);
                  seqx[1] = getseq(namex[1], &len1);
45
                  xbm = (dna)? dbval : pbval;
                  endgaps \approx 0;
                                                        /* 1 to penalize endgaps */
                  ofile = "align.out":
                                                       /* output file */
50
                  nwO:
                                     /* fill in the matrix, get the possible jmps */
                  readimps();
                                     /* get the actual imps */
                                     /* print stats, alignment */
                  print();
                  cleanup(0);
                                    /* unlink any tmp files */
55
```

Table 1 (cont')

```
/* do the alignment, return best score: main()
          * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
          * pro: PAM 250 values
          * When scores are equal, we prefer mismatches to any gap, prefer
  5
          * a new gap to extending an ongoing gap, and prefer a gap in seqx
          * to a gap in seq y.
          */
         nw()
                                                                                                                                 nw
         {
10
                   char
                                       *px, *py;
                                                           /* segs and ptrs */
                   int
                                       *ndely, *dely;
                                                           /* keep track of dely */
                   int
                                       ndelx, delx:
                                                           /* keep track of delx */
                   int
                                       *tmp:
                                                           /* for swapping row0, row1 */
                   int
                                                           /* score for each type */
                                       mis;
15
                   int
                                       ins0, ins1;
                                                           /* insertion penalties */
                   register
                                       id;
                                                           /* diagonal index */
                   register
                                                           /* jmp index */
                   register
                                       *col0, *col1;
                                                           /* score for curr, last row */
                   register
                                                           /* index into seqs */
                                       xx, yy;
20
                   dx = (struct diag *)g calloc("to get diags", len0+len1+1, sizeof(struct diag));
                   ndely = (int *)g_calloc("to get ndely", lenl +1, sizeof(int));
                  dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
25
                   col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
                   ins0 = (dna)? DINS0 : PINS0:
                   ins1 = (dna)? DINS1: PINS1;
30
                   smax = -100000;
                   if (endgaps) {
                             for (col0[0] = dely[0] = -ins0, yy = 1; yy < = len1; yy + +) {
                                       col0[yy] = dely[yy] = col0[yy-1] - ins1;
                                       ndely[yy] = yy;
35
                             col0f01 = 0:
                                                 /* Waterman Bull Math Biol 84 */
                  }
else
                             for (yy = 1; yy < = len1; yy++)
40
                                       dely[yy] = -ins0;
                  /* fill in match matrix
                  for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
45
                             /* initialize first entry in col
                             if (endgaps) {
                                       if (xx = = 1)
                                                 col1[0] = delx = -(ins0+ins1):
50
                                      else
                                                col1[0] = delx = col0[0] - ins1:
                                       ndelx = xx:
                             else {
55
                                      col1[0] = 0;
                                      delx = -ins0;
                                      ndelx = 0;
                            }
60
```

...nw

WO 02/08288 PCT/US01/21066

Table 1 (cont')

```
for (py = seqx[1], yy = 1; yy \le len1; py++, yy++) {
                                      mis = col0[yy-1];
                                      if (dna)
 5
                                               mis += (xbm[*px-'A']&xbm[*pv-'A'])? DMAT : DMIS;
                                     else
                                               mis += _day[*px-'A'][*py-'A'];
                                     /* update penalty for del in x seq;
10
                                      * favor new del over ongong del
                                      * ignore MAXGAP if weighting endgaps
                                     if (endgaps | | ndely[yy] < MAXGAP) {
                                               if (col0[yy] - ins0 > = dety[yy]) {
    dely[yy] = col0[yy] - (ins0 + ins1);
    idely[yy] = 1;
15
                                               } else {
                                                         dely[yy] -= ins1;
                                                         ndely[yy]++;
20
                                      } else {
                                               if (col0[yy] - (ins0+ins1) > = dely[yy]) \{
                                                         dely[yy] = col0[yy] - (ins0+ins1);
                                                         ndely[yy] = 1;
25
                                               } else
                                                         ndely[yy]++;
                                      }
                                     /* update penalty for del in y seq;
30
                                      * favor new del over ongong del
                                     if (endgaps || ndelx < MAXGAP) {
                                               if (col1[yy-1] - ins0 > = delx) {
                                                         delx = col1[yy-1] - (ins0+ins1);
35
                                                         ndelx = 1:
                                               } else {
                                                         delx -= ins1:
                                                         ndelx++;
40
                                     } else {
                                               if(col1[yy-1] - (ins0+ins1) > = delx) {
                                                         delx = col1[yy-1] - (ins0 + ins1);
                                                         ndelx = 1;
                                               } else
45
                                                         ndelx++:
                                     }
                                     /* pick the maximum score; we're favoring
                                      * mis over any del and delx over dely
50
```

55

60

...nw

WO 02/08288 PCT/US01/21066

```
id = xx - yy + len1 - 1;
                                     if (mis > = delx && mis > = dely[yy])
                                              coll[yy] = mis;
  5
                                     else if (delx >= dely[yy]) {
                                              coll[yy] = delx;
                                               ij = dx[id].ijmp;
                                               if (dx[id], ip.n[0] && (!dna | | (ndelx > = MAXJMP)
                                               && xx > dx[id].jp.x[ij]+MX) \mid | mis > dx[id].score+DINS0)) {
10
                                                        dx[id].ijmp++;
                                                        if (++ij > = MAXJMP) {
                                                                 writejmps(id);
                                                                 ii = dx[id].iimp = 0:
                                                                  dx[id].offset = offset;
15
                                                                 offset += sizeof(struct jmp) + sizeof(offset);
                                                        }
                                              dx[id].jp.n[ij] = ndelx;
                                              dx[id].jp.x[ij] = xx;
20
                                              dx[id].score = delx;
                                     else {
                                              col1[yy] = dely[yy];
                                              ij = dx[id].ijmp;
25
                  if (dx[id].jp.n[0] && (!dna | | (ndely[yy] > = MAXJMP)
                                              && xx > dx[id].ip.x[ii]+MX) \mid | mis > dx[id].score+DINS0)) 
                                                        dx[id].ijmp++;
                                                        if (++ij > = MAXJMP) {
                                                                 writejmps(id);
30
                                                                 ij = dx[id].ijmp = 0;
                                                                 dx[id].offset = offset;
                                                                 offset += sizeof(struct jmp) + sizeof(offset);
                                                        }
35
                                              dx[id].jp.n[ij] = -ndely[yy];
                                              dx[id].jp.x[ij] = xx;
                                              dx[id].score = delv[vv]:
                                     if (xx == len0 && yy < len1) {
40
                                              /* last col
                                               */
                                              if (endgaps)
                                                        col1[yy] -= ins0+ins1*(len1-yy);
                                              if (coll[yy] > smax) {
45
                                                        smax = coll[yy];
                                                        dmax = id;
                                              }
                                     }
50
                           if (endgaps && xx < len0)
                                     col1[yy-1] -= ins0+ins1*(len0-xx);
                           if (col1[yy-1] > smax) {
                                     smax = col1[yy-1];
                                     dmax = id;
55
                           tmp = col0; col0 = col1; col1 = tmp;
                  (void) free((char *)ndely);
                  (void) free((char *)dely);
60
                  (void) free((char *)col0);
(void) free((char *)col1);
                                                                 3
```

Page 38 of 359

WO 02/08288

```
* print() -- only routine visible outside this module
 5
          * static:
          * getmat() -- trace back best path, count matches: print()
          * pr_align() -- print alignment of described in array p[]: print()
          * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
          * nums() -- put out a number line: dumpblock()
10
          * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
          * stars() - -put a line of stars: dumpblock()
          * stripname() - strip any path and prefix from a sequame
15
         #include "nw.h"
         #define SPC
         #define P LINE 256
                                      /* maximum output line */
         #define P SPC 3
                                      /* space between name or num and seq */
20
         extern
                  day[26][26];
         int
                  olen;
                                      /* set output line length */
         FILE
                  *fx;
                                      /* output file */
25
         print()
                                                                                                                            print
         {
                  int
                                                         /* overlap */
                            lx, ly, firstgap, lastgap;
                  if ((fx = fopen(ofile, "w")) == 0) {
    fprintf(stderr, "%s: can't write %s\n", prog, ofile);
30
                            cleanup(1):
                  fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
                  fprintf(fx, "< second sequence: %s (length = %d)\n", namex[1], len1);
35
                  olen = 60;
                  1x = len0;
                  ly = len1;
                  firstgap = lastgap = 0;
                  if (dmax < len1 - 1) {
                                               /* leading gap in x */
40
                            pp[0].spc = firstgap = len1 - dmax - 1;
                            ly = pp[0].spc;
                  else if (dmax > len1 - 1) { /* leading gap in y */
                            pp[1].spc = firstgap = dmax - (len1 - 1);
45
                            1x -= pp[1].spc;
                  if (dmax0 < len0 - 1) { /* trailing gap in x */
                            lastgap = len0 - dmax0 - 1;
                            lx -= lastgap;
50
                  else if (dmax0 > len0 - 1) { /* trailing gap in y */
                            lastgap = dmax0 - (len0 - 1);
                            ly -= lastgap;
55
                  getmat(lx, ly, firstgap, lastgap);
                  pr align();
        }
```

WO 02/08288

```
Table 1 (cont')
```

```
* trace back the best path, count matches
         */
        static
 5
        getmat(lx, ly, firstgap, lastgap)
                                                                                                                    getmat
                 int
                           lx, 1y;
                                                       /* "core" (minus endgaps) */
                 int
                           firstgap, lastgap;
                                                       /* leading trailing overlap */
        {
                 int
                                    nm, i0, i1, siz0, siz1;
10
                 char
                                    outx[32];
                 double
                                    pct;
                                    n0, n1;
                 register
                 register char
                                    *p0, *p1;
15
                 /* get total matches, score
                 i0 = i1 = siz0 = siz1 = 0;
                 p0 = seqx[0] + pp[1].spc;
                 p1 = seqx[1] + pp[0].spc;
20
                 n0 = pp[1].spc + 1;
                 n1 = pp[0].spc + 1;
                 nm = 0;
                 while ( *p0 && *p1 ) {
25
                           if (siz0) {
                                    p1++:
                                    n1++;
                                    siz0-:
30
                           else if (siz1) {
                                    p0++;
                                    n0++:
                                    siz1-;
35
                           else {
                                    if (xbm[*p0-'A']&xbm[*p1-'A'])
                                             nm++;
                                    if (n0++==pp[0].x[i0])
                                    siz0 = pp[0].n[i0++];
if (n1++==pp[1].x[i1])
40
                                             siz1 = pp[1].n[i1++];
                                    p0++:
                                    p1++;
                           }
45
                 }
                 /e pct homology:
                  * if penalizing endgaps, base is the shorter seq
                  * else, knock off overhangs and take shorter core
50
                  */
                 if (endgaps)
                           lx = (len0 < len1)? len0 : len1:
                 else
                           1x = (1x < 1y)? 1x : 1y;
55
                 pct = 100.*(double)nm/(double)lx;
                 fprintf(fx, "\n");
                 fprintf(fx, " < %d match%s in an overlap of %d; %.2f percent similarity\n",
                           nm, (nm = = 1)? "" : "es", lx, pct);
60
```

```
fprintf(fx, "<gaps in first sequence: %d", gapx);
                                                                                                                         ...getmat
                   if (gapx) {
                             (void) sprintf(outx, " (%d %s%s)",
                                       ngapx, (dna)? "base": "residue*, (ngapx == 1)? "": "s");
  5
                             fprintf(fx, "%s", outx);
                   fprintf(fx, ", gaps in second sequence: %d", gapy);
                   if (gapy) {
                             (void) sprintf(outx, " (%d %s%s)",
10
                                       ngapy, (dna)? "base": "residue", (ngapy == 1)? "": "s");
                             fprintf(fx, "%s", outx);
                   if (dna)
                             fprintf(fx,
15
                             "\n < score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
                             smax, DMAT, DMIS, DINSO, DINS1);
                   else
                             fprintf(fx,
                             "\n < score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
20
                             smax, PINSO, PINS1);
                   if (endgaps)
                             forintf(fx.
                              "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",</p>
                             firstgap, (dna)? "base": "residue", (firstgap == 1)? "": "s", lastgap, (dna)? "base": "residue", (lastgap == 1)? "": "s");
25
                   else
                             fprintf(fx, "<endgaps not penalized\n");
         3
30
          static
                             nm;
                                                 /* matches in core - for checking */
          static
                             Imax:
                                                 /* lengths of stripped file names */
          static
                             ij[2];
                                                 /* jmp index for a path */
          static
                             nc[2];
                                                 /* number at start of current line */
          static
                             ni[2];
                                                 /* current elem number -- for gapping */
35
          static
                             siz[2];
          static char
                             *ps[2];
                                                 /* ptr to current element */
          static char
                             *po[2];
                                                 /* ptr to next output char slot */
          static char
                             out[2][P LINE]; /* output line */
          static char
                            star[P_LINE];
                                                 /* set by stars() */
40
          * print alignment of described in struct path pp[]
         static
45
         pr_align()
                                                                                                                         pr align
                   int
                                                 /* char count */
                                       nn:
                   int
                                       more;
                   register
                                       i:
50
                   for (i = 0, lmax = 0; i < 2; i++)
                            nn = stripname(namex[i]);
                             if (nn > lmax)
                                       lmax = nn:
55
                            nc[i] = 1;
                            ni[i] = 1;
                            siz[i] = ij[i] = 0;

ps[i] = seqx[i];
60
                            po[i] = out[i];
                                                                    }
```

WO 02/08288

```
...pr align
                 for (nn = nm = 0, more = 1; more;)
                          for (i = more = 0; i < 2; i++)
  5
                                    * do we have more of this sequence?
                                    */
                                   if (!*ps[i])
                                           continue;
 10
                                   more++:
                                   if (pp[i].spc) { /* leading space */
                                            *po[i]++ = ' ';
                                            pp[i].spc~;
 15
                                   20
                                   else {
                                                    /* we're putting a seq element
                                            *po[i] = *ps[i];
                                            if (islower(*ps[i]))
                                                    *ps[i] = toupper(*ps[i]);
25
                                           po[i]++;
                                           ps[i]++;
                                            * are we at next gap for this seq?
30
                                           if (ni[i] == pp[i].x[ij[i]]) \{
                                                     * we need to merge all gaps
                                                     * at this location
35
                                                     */
                                                    siz[i] = pp[i].n[ij[i]++];
                                                    while (ni[i] == pp[i].x[ij[i]])
                                                             siz[i] += pp[i].n[ij[i]++];
40
                                           ni[i]++;
                                  }
                          if(++nn = = olen | | !more && nn) {
                                  dumpblock();
45
                                  for (i = 0; i < 2; i++)
                                           po[i] = out[i];
                                  nn = 0;
                          }
                 3
50
        }
         * dump a block of lines, including numbers, stars: pr align()
55
        static
        dumpblock()
                                                                                                        dumpblock
        {
                 register i:
60
                 for (i = 0; i < 2; i++)
                         *po[i]-- = '\0';
```

WCG268268 [IBe://E-AV06206236 opc.]

PCT/US01/21066

```
...dumpblock
                   (void) putc('\n', fx);
                   for (i = 0; i < 2; i++) {
  5
                            if (*out[i] && (*out[i] != ' ' | | *(po[i]) != ' ')) {
                                     if (i == 0)
                                               nums(i);
                                     if (i == 0 && *out[1])
 10
                                     putline(i);
                                     if (i = = 0 && *out[1])
                                               fprintf(fx, star);
                                     if (i == 1)
                                               nums(i);
 15
                            }
                  }
         }
20
          * put out a number line: dumpblock()
         static
         nums(ix)
                                                                                                                       nums
                            ix;
                                     /* index in out[] holding seq line */
                  int
25
                  char
                                     nline[P_LINE];
                  register
                                     i, j;
                  register char
                                     *pn, *px, *py;
30
                  for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
                            *pn = ' ';
                  for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
                           if (*py == ' ' | | *py == '-')
*pn = ' ';
35
                           else {
                                     if (i%10 == 0 || (i == 1 && nc[ix]!= 1)) {
                                              j = (i < 0)? \cdot i : i;
                                              for (px = pn; j; j /= 10, px-)
                                                        px = j\%10 + '0';
40
                                              if (i < 0)
                                                        *px = '-';
                                     élse
                                               *pn = ' ';
45
                                     i++:
                           }
                  *pn = '\0';
                  nc[ix] = i;
50
                  for (pn = nline; *pn; pn++)
                           (void) putc(*pn, fx);
                  (void) putc('\n', fx);
         }
55
          * put out a line (name, [num], seq, [num]): dumpblock()
         static
         putline(ix)
                                                                                                                     putline
60
                  int
                           ix;
                                                        {
```

Table 1 (cont')

```
...putline
                   int
                                      i;
                   register char
                                      *рх;
  5
                   for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
                             (void) putc(*px, fx);
                   for (; i < lmax+P_SPC; i++)
                             (void) putc(' ', fx);
10
                   /* these count from 1;
                    * ni[] is current element (from 1)
                   * nc[] is number at start of current line
15
                   for (px = out[ix]; *px; px++)
                            (void) putc(*px&0x7F, fx);
                   (void) putc('\n', fx);
         }
20
          * put a line of stars (seqs always in out[0], out[1]); dumpblock()
         static
25
         stars()
                                                                                                                            stars
                   register char
                                      *p0, *p1, cx, *px;
30
                   if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
!*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
                            return;
                   px = star;
                   for (i = 1max+P_SPC; i; i--)
35
                            *px++= ' ';
                   for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
                            if (isalpha(*p0) && isalpha(*p1)) {
40
                                      if (xbm[*p0-'A']&xbm[*p1-'A']) {
                                                cx = '*';
                                                nm++;
                                      élse if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
cx = '.';
45
                                      else
                                                cx = ' ';
                            else
50
                                      cx = ' ':
                            *px++=cx;
                   *px++ = 'n';
                  *px = '\0';
55
```

60

WO 02/08288

PCT/US01/21066

```
Table 1 (cont')
         * strip path or prefix from pn, return len: pr_align()
        static
 5
        stripname(pn)
                                                                                                       stripname
                 char *pn; /* file name (may be path) */
        {
                 register char *px, *py;
10
                py = 0;
                for (px = pn; *px; px++)
if (*px == '/')
                                 py = px + 1;
                if (py)
15
                         (void) strcpy(pn, py);
                return(strlen(pn));
        }
20
25
30
35
40
45
50
55
60
```

Table 1 (cont')

WO 02/08288

PCT/US01/21066

```
* cleanup() -- cleanup any tmp file
          * getseq() -- read in seq, set dna, len, maxlen
          * g calloc() -- calloc() with error checkin
  5
          * readjmps() -- get the good jmps, from tmp file if necessary
          * writejmps() - write a filled array of jmps to a tmp file: nw()
         #include "nw.h"
         #include < sys/file.h>
10
                   *jname = "/tmp/homgXXXXXX";
                                                                      /* tmp file for jmps */
         FILE
         int
                   cleanup();
                                                                      /* cleanup tmp file */
15
         long
                   Iscek():
          * remove any tmp file if we blow
          */
20
         cleanup(i)
                                                                                                                             cleanup
                             i:
         {
                   if (fj)
                             (void) unlink(jname);
25
                   exit(i);
         }
          * read, return ptr to seq, set dna, len, maxlen
* skip lines starting with ';', '<', or '>'
30
          * seq in upper or lower case
         char
         getseq(file, len)
                                                                                                                               getseq
35
                             *file;
                                       /* file name */
                   char
                   int
                             *len:
                                       /* seq len */
         {
                   char
                                       line[1024], *pseq;
                   register char
                                        *px, *py;
40
                   int
                                        natge, tlen;
                   FILE
                                        *fp;
                   if ((fp = fopen(file, "r")) == 0) {
                             fprintf(stderr, "%s: can't read %s\n", prog, file);
45
                             exit(1):
                   tlen = natgc = 0;
                   while (fgcts(line, 1024, fp)) {
                             if (*line == ';' || *line == '<' || *line == '>')
50
                                       continue:
                             for (px = line; *px != '\n'; px++)

if (isupper(*px) || islower(*px))
                                                 tlen++:
55
                   if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
                             fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen +6, file);
                             exit(1);
                   pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
60
```

```
...getseq
                  py = pseq + 4;
                  *Ien = tlen:
                  rewind(fp);
  5
                  while (fgets(line, 1024, fp)) {
                           if (*line == ';' || *line == '<' || *line == '>')
                                    continue;
                           for (px = line; *px != '\n'; px++) {
10
                                    if (isupper(*px))
                                              *py++ = *px;
                                    else if (islower(*px))
                                    *py++ = toupper(*px);
if (index(*ATGCU*,*(py-1)))
15
                                              natgc++;
                           }
                  *py++ = '\0';
                  *py = '\0';
20
                  (void) fclose(fp);
                  dna = natgc > (tlen/3);
                  return(pseq+4);
        }
25
        char
                                                                                                                   g calloc
         g_calloc(msg, nx, sz)
                  char
                           *msg;
                                              /* program, calling routine */
                  int
                                              /* number and size of elements */
                           nx, sz;
30
                                    *px, *calloc();
                  char
                  if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
                                    fprintf(stderr, "%s: g_calloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
35
                                    exit(1);
                 return(px);
        }
40
         * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
                                                                                                                 readjmps
        readjmps()
45
                                    fd = -1:
                 int
                 int
                                    siz, i0, i1;
                 register i, j, xx;
50
                 if (fj) {
                           (void) fclose(fj);
                           if ((fd = open(iname, O RDONLY, 0)) < 0) {
                                    fprintf(stderr, "%s: can't open() %s\n", prog, iname);
                                    cleanup(1);
55
                 for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; : i++) {
                           while (1) {
                                    for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].ip.x[j] >= xx; j--)
60
```

```
... readimps
                                     if (j < 0 && dx[dmax].offset && fj) {
                                               (void) lseek(fd, dx[dmax].offset, 0);
                                               (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
  5
                                               (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
                                               dx[dmax].ijmp = MAXJMP-1;
                                     }
                                     else
                                               break;
 10
                            if (i > = JMPS) {
                                     fprintf(stderr, "%s: too many gaps in alignment\n", prog);
                                     cleanup(1);
                            \inf_{i} (i > = 0) 
15
                                     siz = dx[dmax].jp.n[j];
                                     xx = dx[dmax].jp.x[j];
                                     dmax += siz:
                                     if (siz < 0) {
                                                                 /* gap in second seq */
20
                                               pp[1].n[i1] = -siz;
                                               xx += siz:
                                               /* id = xx - yy + len1 - 1
                                               pp[1].x[i1] = xx - dmax + len1 - 1;
25
                                               gapy++;
                                               ngapy -= siz;
         /* ignore MAXGAP when doing endgaps */
                                               siz = (-siz < MAXGAP | | endgaps)? -siz : MAXGAP;
30
                                     else if (siz > 0) { /* gap in first seq */
                                              pp[0].n[i0] = siz;
                                              pp[0].x[i0] = xx;
                                              gapx++;
35
                                               ngapx += siz;
         /* ignore MAXGAP when doing endgaps */
                                               siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
                                              i0++;
                                     }
40
                           }
                           else
                                     break:
                  }
45
                  /* reverse the order of jmps
                  for (j = 0, i0--; j < i0; j++, i0--)
                           i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
                           i = pp[0].x[i]; pp[0].x[i] = pp[0].x[i0]; pp[0].x[i0] = i;
50
                  for (j = 0, i1--; j < i1; j++, i1--) {
                           i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
                           i = pp[1].x[i]; pp[1].x[i] = pp[1].x[i1]; pp[1].x[i1] = i;
55
                  if (fd >= 0)
                           (void) close(fd);
                  if (fi) {
                           (void) unlink(jname):
                           f_j = 0;
60
                           offset = 0:
                                                       }
```

WO 02/08288

PCT/US01/21066

```
* write a filled jmp struct offset of the prev one (if any): nw()
 5
        writejmps(ix)
                                                                                                              writejmps
                 int
                          ix;
                 char
                           *mktemp();
10
                 if (!fj) {
                           if (mktemp(jname) < 0) {
                                    fprintf(stderr, *%s: can't mktemp() %s\n", prog, jname);
                                    cleanup(1);
                          15
                           }
20
                 (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
(void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
        }
25
30
35
40
45
50
55
60
```

Page 49 of 359

WO 02/08288

Table 2

PRO XXXXXXXXXXXXXX

(Length = 15 amino acids)

Comparison Protein

XXXXXYYYYYYY

(Length = 12 amino acids)

5 % amino acid sequence identity =

> (the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

10 5 divided by 15 = 33.3 %

Table 3

PRO

XXXXXXXXX

(Length = 10 amino acids)

15 Comparison Protein XXXXXYYYYYYZZYZ

(Length = 15 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined 20 by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 10 = 50%

Table 4

25

PRO-DNA

NNNNNNNNNNNN

(Length = 14 nucleotides)

Comparison DNA

NNNNNLLLLLLLLLL

(Length = 16 nucleotides)

% nucleic acid sequence identity =

30

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

6 divided by 14 = 42.9%

35

WC0208088 [Re-//E-AV-00208288 opc] Page 50 of 356

WO 02/08288 PCT/US01/21066

Table 5

PRO-DNA NNNNNNNNNN (Length = 12 nucleotides)
Comparison DNA NNNNLLLVV (Length = 9 nucleotides)

5 % nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

10 4 divided by 12 = 33.3%

15

20

25

30

35

II. Compositions and Methods of the Invention

A. Full-Length PRO Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

B. PRO Polypeptide Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative

10

15

20

25

WO 02/08288 PCT/US01/21066

mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Outdance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligomucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

	Original <u>Residue</u>	Exemplary Substitutions	Preferred Substitutions
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
10	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe;	-
15		norleucine	leu
	Leu (L)	norleucine; ile; val;	
		met; ala; phe	ile
20	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
	Ser (S)	thr	thr
25	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe;	
		ala; norleucine	leu

30 Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- 35 (1) hydrophobic: norleucine, met, ala, val, leu, ile;
 - (2) neutral hydrophilic: cys, ser, thr;
 - (3) acidic: asp, glu;
 - (4) basic: asn, gln, his, lys, arg;
 - (5) residues that influence chain orientation: gly, pro; and
- 40 (6) aromatic; trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (sitedirected) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl.
Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al.,

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA. 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacety)-2-phenylethane, glutaraldehyde, N-inydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional materimides such as bis-N-male/mido-1,8-octane and agents such as methyl-3-f(o-azidophenyl/dinic) propionimidate.

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and asparryl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the a-amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, <u>Proteins: Structure and Molecular Properties</u>, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acevylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through chances at the DNA level, particularly by mutatine the DNA encoding

the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, <u>CRC Crit. Rev. Biochem.</u>, pp. 259-306 (1981).

5

10

15

20

25

30

35

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-plycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypentide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8;2159-2165 (1983)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:12O4-1210 (1988)]; the KT3 epitope peptide [Martin et al., Seinece, 255:192-194 (1992)]; an α-ubulin epitope peptide [Skinner et al., L Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proce. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgGi molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27,

1995.

5

10

15

20

25

30

35

D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis. W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., §5:2149-2154 (1963)]. In vitro protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to nrockue the full-leneth PRO.

Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., <u>Molecular Cloning: A Laboratory Manual</u> (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., <u>supra:</u> Dietfenbach et al., <u>PCR Primer: A Laboratory Manual</u> (Cold Spring Harbor Laboratory Press, 1995).

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ³²P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identify (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and

processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

5

10

15

20

25

30

35

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butter, ed. (IRL Press, 1991) and Sambrook et al., SUDTA.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl₃, CaPO₆, liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., <u>supra</u>, or electroporation is generally used for prokaryotes. Infection with Agrobacterium tumefaciens is used for transformation of certain plant cells, as described by Shaw et al., <u>Gene</u>, <u>23</u>:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, <u>Virology</u>, <u>22</u>:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., <u>J. Bact.</u>, <u>130</u>:946 (1977) and Hsiao et al., <u>Proc. Natl. Acad. Sci. (USA)</u>, <u>76</u>:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyomithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., <u>Methods in Enzymology</u>, 185:527-537 (1990) and Mansour et al., <u>Nature</u>, 336:348-332 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as E. coli. Various E. coli strains are publicly available, such as E. coli K12 strain MM294 (ATCC 31,446); E. coli X1776 (ATCC 31,537); E. coli strain w3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as Escherichia, e.g., E. coli, Enterobacteri, Enviria, Klebsiella, Protexs, Salmonella, e.g., Salmonella typhimurium, Serratia, e.g., Serratia marcescans, and Shigella, as well as Bacilli such as B. subtilis and B. lichentiformis (e.g., B. lichentiformis 41P disclosed in DD 266,710 published 12 April 1989), Pseudomonas such as P. enruginosa, and Streptomyces. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including E. coli W3110 strain 12A2, which has the complete genotype ton Apri. E. coli W3110 strain 2FA, Which has the complete genotype ton Apri. E. coli W3110 strain 2FA, Which has the complete genotype ton Apri. E. coli W3110 strain 2FA, Which has the complete genotype ton Apri. E. coli W3110 strain 2FA, Which has the complete genotype ton Apri. E. coli W3110 strain 2FA.

55,244), which has the complete genotype tonA ptr3 phoA E15 (argF-lac)169 degP ompT kart', E. coli W3110 strain 37D6, which has the complete genotype tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 livG kart', E. coli W3110 strain 40B4, which is strain 37D6 with a non-kanamyto resistant degP deletion mutation; and an E. coli strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, in vitro metbods of cloning, e.g., PCR or ofter nucleic acid polymerase reactions, are suitable.

5

10

15

20

25

30

35

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. Saccharomyces cerevisiae is a commonly used lower eukaryotic host microorganism. Others include Schizosaccharomyces pombe (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); Kluyveromyces hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., K. lactis (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), K. fragilis (ATCC 12,424), K. bulgaricus (ATCC 16,045), K. wickeramii (ATCC 24,178), K. waltii (ATCC 56,500), K. drosophilarum (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), K. thermotolerans, and K. marxianus; yarrowia (EP 402,226); Pichia pastoris (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); Candida; Trichoderma reesia (EP 244,234); Neurospora crassa (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); Schwamiomyces such as Schwanniomyces occidentalis (EP 394,538 published 31 October 1990); and filamentous fungi such as. e.g., Neurospora, Penicillium, Tolypocladium (WO 91/00357 published 10 January 1991), and Aspergillus hosts such as A. nidulans (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and A. niger (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of Hansenula, Candida, Kloeckera, Pichla, Saccharomyces, Torulopsis, and Rhodotorula. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as Drosophila S2 and Spodoptera St9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CVI line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., <u>J. Gen Virol.</u>, 36:59 (1977)); Chinese hamster ovary cells/DHFR (CHO, Urlaub and Chasin, <u>Proc. Natl. Acad. Sci. USA</u>, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, <u>Biol. Reprod.</u>, 22:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep Q2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the allkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including Saccharomyces and Klinyveromyces α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the C. albicans glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-adanine racemase for Bacilli.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHTR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., <u>Froc., Natl., Acad., Sci., USA.</u>, 77:4216 (1980). A suitable selection gene for use in yeast is the trp1 gene present in the yeast plasmid YRp7 [Stinchcomb et al., <u>Nature</u>, 282:39 (1979); Kingsman et al., <u>Gene</u>, 7:141 (1979); Tschemper et al., <u>Gene</u>, 10:157 (1980)]. The trp1 gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β-lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a typiophan (trp) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

promoters such as the tac promoter [deBoer et al., <u>Proc. Natl. Acad. Sci. USA</u>, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3phosphoglycerate kinase [Hitzeman et al., <u>I. Biol. Chem.</u>, 255:2073 (1980)] or other glycolytic enzymes [Hess
et al., <u>I. Adv. Enzyme. Reg.</u>, 7:149 (1968); Holland, <u>Biochemistry</u>, 17:4900 (1978)], such as enolase,
glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose
isomerase, and efucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73.657.

PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, e-fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., <u>Nature</u>, 293:620-625 (1981); Mantei et al., <u>Nature</u>, 281:40-46 (1979); EP 117,060; and EP 117,058.

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, <u>Proc. Natl. Acad. Sci. USA</u>, 77:5201-5205 (1980)], dot blotting (DNA analysis), or in situ hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephades G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitopetagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice. Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

E. Uses for PRO

Nucleotide sequences (or their complement) encoding PRO have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO nucleic acid will also be useful for the preparation of PRO polypeptides by the recombinant techniques described herein.

The full-length native sequence PRO gene, or portions thereof, may be used as hybridization probes for

15

20

25

30

35

WO 02/08288 PCT/US01/21066

a cDNA library to isolate the full-length PRO cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of PRO or PRO from other species) which have a desired sequence identity to the native PRO sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be determined without undue experimentation or from genomic sequences sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence PRO. By way of example, a screening method will comprise isolating the coding region of the PRO gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ³³P or ³⁵S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the PRO gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the PRO nucleic acids include antisense or sense oligonucleotides comprising a singe-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO mRNA (sense) or PRO DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of PRO DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. The antisense oligonucleotides thus may be used to block expression of PRO proteins. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable in vivo (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target mucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO4-mediated DNA transfection,

Page 82 of 359

electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either in vivo or ex vivo. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCTSA, DCTSB and DCTSC (see WO 90/13641).

5

10

15

20

25

30

35

Sense or antisense oligomucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endocenous linase.

Antisense or sense RNA or DNA molecules are generally at least about 5 bases in length, about 10 bases in length, about 20 bases in length, about 25 bases in length, about 30 bases in length, about 45 bases in length, about 50 bases in length, about 55 bases in length, about 65 bases in length, about 65 bases in length, about 55 bases in length, about 65 bases in length, about 75 bases in length, about 80 bases in length, about 85 bases in length, about 80 bases in length, about 80

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO coding sequences.

Nucleotide sequences encoding a PRO can also be used to construct hybridization probes for mapping the gene which encodes that PRO and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as in situ hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for PRO encode a protein which binds to another protein (example, where the PRO is a receptor), the PRO can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor PRO can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native PRO or a receptor for PRO. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, blochemical screening assays, immunoassays and cell based

Page 83 of 359

WO 02/08288 PCT/US01/21066

assays, which are well characterized in the art.

5

10

15

20

25

30

35

Nucleic acids which encode PRO or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding PRO. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for PRO transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding PRO introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding PRO. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of PRO can be used to construct a PRO "knock out" animal which has a defective or altered gene encoding PRO as a result of homologous recombination between the endogenous gene encoding PRO and altered genomic DNA encoding PRO introduced into an embryonic stem cell of the animal. For example, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques. A portion of the genomic DNA encoding PRO can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, Cell, 51:503 (1987) for a description of homologous recombination vectors1. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., Cell, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the PRO polypeptide.

Nucleic acid encoding the PRO polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve in vivo synthesis of a therapeutically effective

genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes in vivo. It has already been shown that short antisense oligomucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zameenik et al., Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

5

10

15

20

25

30

35

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells in vitro, or in vivo in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into manumalian cells in vitro include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred in vivo gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau et al., Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu et al., J. Biol. Chem. 262, 4429-4432 (1987); and Wagner et al., Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson et al., Science 256, 808-813 (1992).

The PRO polypeptides described herein may also be employed as molecular weight markers for protein electrophoresis purposes and the isolated nucleic acid sequences may be used for recombinantly expressing those markers.

The nucleic acid molecules encoding the PRO polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each PRO nucleic acid molecule of the present invention can be used as a chromosome marker.

The PRO polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. PRO nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

The PRO polypeptides described herein may also be employed as therapeutic agents. The PRO polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO product hereof is combined in admixture with a pharmaceutically

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEENTM, PLURONICSTM or PEG.

The formulations to be used for $in\ vivo$ administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The use of interspecies scaling in toxicokinetics" In Toxicokinetics and New Drug Development, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When in vivo administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1 $\mu g/kg/day$ to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO polypeptide, microencapsulation of the PRO polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon-(rhIFN-), interfeuckin-2, and MN rgp120. Johnson et al., Nat. Med. 2:795-799 (1996); Yasuda, Biomed. Ther. 27:1221-1223 (1993); Hora et al., Bio/Technology, 8:755-758 (1990); Cleland. "Design and Production of Single

15

20

25

30

35

WO 02/08288 PCT/US01/21066

Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in <u>Vaccine Design: The Subunit and Adjuvant Approach</u>, Powell and Newman, eds, (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/40073, WO 96/07399; and U.S. Pat. No. 5,654,010.

The sustained-release formulations of these proteins were developed using poly-lactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41.

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agnaists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers

(Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-lacZ reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for \$\begin{array}{c} \mathbb{E}_2 \mathbb{E

10

15

20

25

30

35

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the PRO polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., <u>Current Protocols in Immun.</u>, 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoratiographic analysis. Positive pools are identified and sub-pools are

prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled PRO polypeptide can be photoaffinitylinked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGB and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro- sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

5

10

15

20

25

30

35

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-didotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6;3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem.,: 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of the PRO polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonits include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endomucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, <u>Current Biology</u>, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, supra.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

Diagnostic and therapeutic uses of the herein disclosed molecules may also be based upon the positive functional assay hits disclosed and described below.

F. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies

The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized in vitro.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally,

either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice. Academic Press, (1986) pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HOPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

10

15

20

25

30

35

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, <u>supra</u>]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligomucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Paten: No. 4,816,567; Morrison et al., supreal or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fe region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:333-337 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences

WC0208288 [Re-WE-AVOV208288 opc] Page 72 of 556

PCT/US01/21066

of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human

corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581

(1991)]. The techniques of Cole et al., Monoclonal Antibodies and Cancer Therapy. Alan R. Liss, p. 77 (1985) and Boerner et al., <u>1. Immunol.</u>, <u>147(1)</u>:86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,445,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks et al., <u>Bio/Technology</u> 10.

779-783 (1992); Lonberg et al., Nature 368, 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild et al., Nature Biotechnology 14, 825 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

The antibodies may also be affinity matured using known selection and/or mutagenesis methods as described above. Preferred affinity matured antibodies have an affinity which is five times, more preferably 10 times, even more preferably 20 or 30 times greater than the starting antibody (generally murine, humanized or

human) from which the matured antibody is prepared.

WO 02/08288

5

10

15

20

25

30

35

Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or recentor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 302:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavychain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the

first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

5

10

15

20

25

30

35

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chains(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')₂ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')₇ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from E. coll and chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med., 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab'), molecule. Each Fab' fragment was separately secreted from E. coli and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cyclotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol., 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The *diabody* technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V₁₀) connected to a light-chain variable domain (V₁₀) by a linker which is too short to allow pairing between the two domains on

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., I. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., J. Immunol. 147:60 (1991).

Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein.
Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule
on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fe receptors for IgG
(FcyR), such as FcyRI (CD64), FcyRII (CD32) and FcyRIII (CD16) so as to focus cellular defense mechanisms
to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize cytotoxic
agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and
arm which binds a cytotoxic agent or a radiomclide chelator, such as EOTUBE, DPTA, DOTA, or TETA.
Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptoburyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residuc(s) may be introduced into the Fe region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp. Med., 176: 1191-1195 (1992) and Shopes, J. Immunel., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff et al. Cancer Research, 33: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fe regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989).

Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas acruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated autibodies. Examples include ²¹²Bi, ¹³¹I, ¹³¹In, ⁵⁰Y, and ¹⁸⁶Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidy1-3-(2-pyridy)dithlol) propionate (SPDP), ininiothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disaccinimidyl suberate), aldebydes (such as glutareldedyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., 5cience, 238: 1098 (1987). Carbon-14-labeled 1-isothicyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radiomulceotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., a vidin) that is conjugated to a cytotoxic agent (e.g., a radionucleotide).

8. Immunoliposomes

5

10

15

20

25

30

35

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes comaining the antibody are prepared by methods known in the art, such as described in Epstein et al., <u>Proc. Natl. Acad. Sci.</u> USA. <u>82</u>: 3688 (1985); Hwang et al., <u>Proc. Natl. Acad. Sci. USA. <u>72</u>: 4030 (1980); and U.S. Pat. Nos. 4.485,045 and 4.544.545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5.013,556.</u>

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylchanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon et al., J. National Cancer Inst., 81(19): 1484 (1989).

Pharmaceutical Compositions of Antibodies

5

10

15

20

25

30

35

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e.g., Marasco et al., Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993). The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Reministon's Pharmaceutical Sciences, surva.

The formulations to be used for $in\ vivo$ administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapeules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ cthyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT ™ (injectable microspheres composed of lactic acid-glycolic acid copolymers and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disuffide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

10

15

20

WO 02/08288 PCT/US01/21066

G. Uses for anti-PRO Antibodies

The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, e.g., detecting its expression (and in some cases, differential expression) in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ³H, ¹⁴C, ³²P, ³⁸S, or ¹²³I, a fluorescent or chemiluminescent compound, such as fluorescent isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 124:945 (1962); Pavid et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol, Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem.

Anti-PRO antibodies also are useful for the affinity purification of PRO from recombinant cell culture or natural sources. In this process, the antibodies against PRO are immobilized on a suitable support, such a Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the PRO to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO from the antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

25

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

30

35

EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g., LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or

BLAST-2 (Altschul et al., Methods in Enzymology, 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST or BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., <u>Current Protocols in Molecular Biology</u>, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a Notl site, linked with blunt to SalI hemikinased adaptors, cleaved with Notl, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRKSB is a precursor of pRKSD that does not contain the Sfil site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique Xhol and Notl sites.

EXAMPLE 2: Isolation of cDNA clones by Amylase Screening

5

10

15

20

25

30

35

1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRKSD using reagents and protocols from Life Technologies, Galithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the Sall/NotI linkered cDNA was cloned into XhoI/NotI cleaved vector. pRKSD is a cloning vector that has an sp6 transcription initiation site followed by an Sfill restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

Preparation of random primed cDNA library

A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Scrip Plasmid System, referenced above). In this procedure the double stranded cDNA was

WC0208358 (New YEAV-04205238 opc) Page 19 of 550

PCT/US01/21066

sized to 500-1000 bp, linkered with blunt to Notl adaptors, cleaved with Sfil, and cloned into Sfil/Notl cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

3. Transformation and Detection

WO 02/08288

5

10

15

20

25

30

35

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, e.g. CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, urra3-52, leu2-3, leu2-112, his-3-11, his-3-15, MAL*, SUC*, GAL*. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in sec71, sec62, with truncated sec71 being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TD11p or SSA1p-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz et al., Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser et al., Methods in Yeast Genetics. Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2×10^6 cells/ml (approx. $OD_{\infty 0} = 0.1$) into fresh YEPD broth (500 ml) and regrown to 1×10^6 cells/ml (approx. $OD_{\infty 0} = 0.40.5$).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li_OOCCH₀), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100 µl) with freshly denatured single stranded

WG6268888 | IRE##E AVQ6208288 opc.]

5

10

15

20

25

30

35

WO 02/08288

PCT/US01/21066

Page 30 of 359

salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 μg, vol. < 10 μl) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 μl, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li₂OOCCH₅, pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 μl, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 μl) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting anylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely et al., Anal. Biochem, 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 μ l) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 μ l) was used as a template for the PCR reaction in a 25 μ l volume containing; 0.5 μ l Kentaq (Clontech, Palo Alto, CA); 4.0 μ l 10 mM dNTP's (Perkin Elmer-Cerus); 2.5 μ l Kentaq buffer (Clontech); 0.25 μ l forward oligo 1; 0.25 μ l reverse oligo 2; 12.5 μ l distilled water. The sequence of the forward oligomucleotide 1 was:

5'-TGTAAAACGACGGCCAGT<u>TAAATAGACCTGCAATTATTAATCT</u>-3' (SEQ ID NO:245)
The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:246)
PCR was then performed as follows:

a. Denature 92°C, 5 minutes

b. 3 cycles of: Denature 92°C, 30 seconds

Anneal 59°C. 30 seconds

20

25

30

35

40

WO 02/08288 PCT/US01/21066

			Extend	72°C,	60 seconds
	c.	3 cycles of:	Denature	92°C,	30 seconds
			Anneal	57°C,	30 seconds
5			Extend	72°C,	60 seconds
,	d.	25 cycles of:	Denature	92°C,	30 seconds
			Anneal	55°C,	30 seconds
			Extend	72°C,	60 seconds
10	e.		Hold	4°C	

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.O when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (S µl) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et al., supra. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LiFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

EXAMPLE 4: Isolation of cDNA clones Encoding Human PRO Polypeptides

Using the techniques described in Examples 1 to 3 above, numerous full-length cDNA clones were identified as encoding PRO polypeptides as disclosed herein. These cDNAs were then deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below.

Page 32 of 559

WO 02/08288

Table 7

	<u>Material</u>	ATCC Dep. No.	Deposit Date
	DNA94849-2960	PTA-2306	July 25, 2000
	DNA96883-2745	PTA-544	August 17, 1999
5	DNA96894-2675	PTA-260	June 22, 1999
	DNA100272-2969	PTA-2299	July 25, 2000
	DNA108696-2966	PTA-2315	August 1, 2000
	DNA117935-2801	PTA-1088	December 22, 1999
	DNA119474-2803	PTA-1097	December 22, 1999
10	DNA119498-2965	PTA-2298	July 25, 2000
	DNA119502-2789	PTA-1082	December 22, 1999
	DNA119516-2797	PTA-1083	December 22, 1999
	DNA119530-2968	PTA-2396	August 8, 2000
	DNA121772-2741	PTA-1030	December 7, 1999
15	DNA125148-2782	PTA-955	November 16, 1999
	DNA125150-2793	PTA-1085	December 22, 1999
	DNA125151-2784	PTA-1029	December 7, 1999
	DNA125181-2804	PTA-1096	December 22, 1999
	DNA125192-2794	PTA-1086	December 22, 1999
20	DNA125196-2792	PTA-1091	December 22, 1999
	DNA125200-2810	PTA-1186	January 11, 2000
	DNA125214-2814	PTA-1270	February 2, 2000
	DNA125219-2799	PTA-1084	December 22, 1999
	DNA128309-2825	PTA-1340	February 8, 2000
25	DNA129535-2796	PTA-1087	December 22, 1999
	DNA129549-2798	PTA-1099	December 22, 1999
	DNA129580-2863	PTA-1584	March 28, 2000
	DNA129794-2967	PTA-2305	July 25, 2000
	DNA131590-2962	PTA-2297	July 25, 2000
30	DNA135173-2811	PTA-1184	January 11, 2000
	DNA138039-2828	PTA-1343	February 8, 2000
	DNA139540-2807	PTA-1187	January 11, 2000
	DNA139602-2859	PTA-1588	March 28, 2000
	DNA139632-2880	PTA-1629	April 4, 2000
35	DNA139686-2823	PTA-1264	February 2, 2000
	DNA142392-2800	PTA-1092	December 22, 1999
	DNA143076-2787	PTA-1028	December 7, 1999

Page \$3 of 359

WO 02/08288

Table 7 (cont')

	Material	ATCC Dep. No.	Deposit Date
	DNA143294-2818	PTA-1182	January 11, 2000
	DNA143514-2817	PTA-1266	February 2, 2000
	DNA144841-2816	PTA-1188	January 11, 2000
5	DNA148380-2827	PTA-1181	January 11, 2000
	DNA149995-2871	PTA-1971	May 31, 2000
	DNA167678-2963	PTA-2302	July 25, 2000
	DNA168028-2956	PTA-2304	July 25, 2000
	DNA173894-2947	PTA-2108	June 20, 2000
10	DNA176775-2957	PTA-2303	July 25, 2000
	DNA177313-2982	PTA-2251	July 19, 2000
	DNA57700-1408	203583	January 12, 1999
	DNA62872-1509	203100	August 4, 1998
	DNA62876-1517	203095	August 4, 1998
15	DNA66660-1585	203279	September 22, 1998
	DNA34434-1139	209252	September 16, 1997
	DNA44804-1248	209527	December 10, 1997
	DNA52758-1399	209773	April 14, 1998
	DNA59849-1504	209986	June 16, 1998
20	DNA65410-1569	203231	September 15, 1998
	DNA71290-1630	203275	September 22, 1998
	DNA33100-1159	209377	October 16, 1997
	DNA64896-1539	203238	September 9, 1998
	DNA84920-2614	203966	April 27, 1999
25	DNA23330-1390	209775	April 14, 1998
	DNA32286-1191	209385	October 16, 1997
	DNA35673-1201	209418	October 28, 1997
	DNA43316-1237	209487	November 21, 1997
	DNA44184-1319	209704	March 26, 1998
30	DNA45419-1252	209616	February 5, 1998
	DNA48314-1320	209702	March 26, 1998
	DNA50921-1458	209859	May 12, 1998
	DNA53987	209858	May 12, 1998
	DNA56047-1456	209948	June 9, 1998
35	DNA56405-1357	209849	May 6, 1998
	DNA56531-1648	203286	September 29, 1998
	DNA56865-1491	203022	June 23, 1998

PCT/US01/21066

Page 34 of 359

WO 02/08288

Table 7 (cont')

			Table / (cont /
	DNA57694-1341	203017	June 23, 1998
	DNA57708-1411	203021	June 23, 1998
	DNA57836-1338	203025	June 23, 1998
	DNA57841-1522	203458	November 3, 1998
5	DNA58847-1383	209879	May 20, 1998
	DNA59212-1627	203245	September 9, 1998
	DNA59588-1571	203106	August 11, 1998
	DNA59622-1334	209984	June 16, 1998
	DNA59847-2510	203576	January 12, 1999
10	DNA60615-1483	209980	June 16, 1998
	DNA60621-1516	203091	August 4, 1998
	DNA62814-1521	203093	August 4, 1998
	DNA64883-1526	203253	September 9, 1998
	DNA64889-1541	203250	September 9, 1998
15	DNA64897-1628	203216	September 15, 1998
	DNA64903-1553	203223	September 15, 1998
	DNA64907-1163-1	203242	September 9, 1998
	DNA64950-1590	203224	September 15, 1998
	DNA64952-1568	203222	September 15, 1998
20	DNA65402-1540	203252	September 9, 1998
	DNA65405-1547	203476	November 17, 1998
	DNA66663-1598	203268	September 22, 1998
	DNA66667	203267	September 22, 1998
	DNA66675-1587	203282	September 22, 1998
25	DNA67300-1605	203163	August 25, 1998
	DNA68872-1620	203160	August 25, 1998
	DNA71269-1621	203284	September 22, 1998
	DNA73736-1657	203466	November 17, 1998
	DNA73739-1645	203270	September 22, 1998
30	DNA76400-2528	203573	January 12, 1999
	DNA76532-1702	203473	November 17, 1998
	DNA76541-1675	203409	October 27, 1998
	DNA79862-2522	203550	December 22, 1998
	DNA81754-2532	203542	December 15, 1998
35	DNA81761-2583	203862	March 23, 1999
	DNA83500-2506	203391	October 29, 1998
	DNA84210-2576	203818	March 2, 1999

20

25

35

WO 02/08288 PCT/US01/21066

Table 7 (cont')

	DNA86571-2551	203660	February 9, 1999
	DNA92218-2554	203834	March 9, 1999
	DNA92223-2567	203851	March 16, 1999
	DNA92265-2669	PTA-256	June 22, 1999
5	DNA92274-2617	203971	April 27, 1999
	DNA108760-2740	PTA-548	August 17, 1999
	DNA 108792-2753	PTA-617	August 31, 1999
	DNA111750-2706	PTA-489	August 3, 1999
	DNA119514-2772	PTA-946	November 9, 1999
10	DNA125185-2806	PTA-1031	December 7, 1999

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

The assignce of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

EXAMPLE 5: Isolation of cDNA clones Encoding Human PRO6004, PRO5723, PRO3444, and PRO9940

DNA molecules encoding the PRO840, PRO1338, PRO6004, PRO5723, PRO3444, and PRO9940

30 polypeptides shown in the accompanying figures were obtained through GenBank.

EXAMPLE 6: Use of PRO as a hybridization probe

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue eDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following

high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an acueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can 5 — then be identified using standard techniques known in the art.

EXAMPLE 7: Expression of PRO in E. coli

10

15

20

25

30

35

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in E. coli.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from E. coli; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected E. coll strain using the methods described in Sambrook et al., <u>supra</u>. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in E. colf in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an E. colf host based on strain 52 (W3110 fuhA(tonA) lon galE rpolits(thpRs) clpP(lacle). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with haking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.5°T g (NH_Q)₂SO₂, 0.71 g sodium citrate=2H2O, 1.0°T g KCl, 5.36 g Difto yeast extract, 5.36 g

WC0208088 (IRe///E-AVOV206288 opc) Page 87 of 556

WO 02/08288 PCT/US01/21066

Sheffield hyease SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSQ₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guaridine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1 mM and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guaridine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is cluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 mm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros RI/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO potypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 8: Expression of PRO in mammalian cells

5

10

15

20

25

30

35

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector.

Page 38 of 359

WC6268888 (IBH // E-AV 06268288 opc)

5

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

Optionally, the PRO DNA is ligated into pRKS with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called pRKS-PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-PRO DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/mi ³⁵-cysteine and 200 µCi/mi ³⁶-sembinine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrae et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell peller for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 µg/ml bovine insulin and 0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as CaPO₄ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ³⁵S-methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the PRK5 vector. The subclone insert can underge PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells

can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni²⁺-chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

5

10

15

20

25

30

35

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., <u>Current Protocols of Molecular Biology</u>, Unit 3. 16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., <u>Nucl. Acids Res.</u> 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect (Ogiagon), Dosper or Fugene (Boehringer Mannheim). The cells are grown as described in Lucas et al., supra. Approximately 3 x 107 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μm filtered PS20 with 5% 0.2 μm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3 x 105 cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2 x 106 cells/mL. On day 0, the cell number pH ie determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 \(mu\)m filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mamiltol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fe-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 µL of 1 ml Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 9: Expression of PRO in Yeast

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 10: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding.

Page 91 of 359

PCT/US01/21066

WC6268888 (IBH //E-AVO6268288 opc)

5

10

15

20

30

35

WO 02/08288

the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGoldTM virus DNA (Pharmingen) into Spodoptera frugiperda (*Sf9*) cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7-9; 12.5 mM MgCl₃; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M ECD, and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatunt is diluted 50-fold including buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A₂₆₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A₃₆₀ baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-conjugated to alkaline phosphatase (Olagen). Fractions containing the eluted His₁₆-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

25 Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 11: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, <u>supra</u>. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

additional immunization injections. Scrum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63 AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intrapertioneally into syngencic Balble mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 12: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with animonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSETM (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration

Page 93 of 359

WO 02/08288 PCT/US01/21066

of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

EXAMPLE 13: Drug Screening

WC6268888 (IBH //E-AVO6268288 opc)

5

10

15

20

25

30

35

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (I) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antieenic determinants with PRO polypeptide.

EXAMPLE 14: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (i.e., a PRO polypeptide) or of small molecules with which they interact, e.g., agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide in ψ_{ij} (c.f., Hodeson,

Bio/Technology, 9: 19-21 (1991)).

5

10

15

20

25

30

35

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda et al., J. Biochemi, 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

EXAMPLE 15: Pericyte c-Fos Induction (Assay 93)

This assay shows that certain polypeptides of the invention act to induce the expression of c-fos in pericyte cells and, therefore, are useful not only as diagnostic markers for particular types of pericyte-associated tumors but also for giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors. Induction of c-fos expression in pericytes is also indicative of the induction of angiogenesis and, as such, PRO polypeptides capable of inducing the expression of c-fos would be expected to be useful for the treatment of conditions where induced angiogenesis would be beneficial including, for example, wound healing, and the like. Specifically, on day 1, pericytes are received from VEC Technologies and all but 5 ml of media is removed from flask. On day 2, the pericytes are treated with 100 µl of PRO polypeptide test samples and controls (positive control = DME+5% serum +/- PDGF at 500 ng/ml; negative control = protein 32). Replicates are averaged and SD/CV are determined. Fold increase over Protein 32 (buffer control) value indicated by chemiltuminescence units (RLU) luminometer reading verses frequency is plotted on a histogram. Two-fold above Protein 32 value is considered positive for the assay. ASY Matrix: Growth media = low glucose DMEM = 20% FBS + 1X pen strep + 1X fungizone. Assay Media = low glucose DMEM + 5% FBS.

The following polypeptides tested positive in this assay: PRO982, PRO1160, PRO1187, and PRO1329.

WC0208088 [IRe///E-AVOV208288 opc] Page 95 of 355

WO 02/08288 PCT/US01/21066

EXAMPLE 16: Chondrocyte Re-differentiation Assay (Assay 110)

5

10

15

20

25

30

35

This assay shows that certain polypeptides of the invention act to induce redifferentiation of chondrocytes, therefore, are expected to be useful for the treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis. The assay is performed as follows. Porcine chondrocytes are isolated by overnight collagenase digestion of articulary cartilage of metacar-pophalangeal joints of 4-6 month old female pigs. The isolated cells are then seeded at 25,000 cells/m² in Ham F-12 containing 10% FBS and 4, μ /ml gentamycin. The culture media is changed every third day and the cells are then seeded in 96 well plates at 5,000 cells/well in 100 μ l of the same media without serum and 100 μ l of the test PRO polypeptide, 5 nM staurosporin (positive control) or medium alone (negative control) is added to give a final volume of 200 μ l/well. After 5 days of incubation at 37°C, a picture of each well is taken and the differentiation state of the chondrocytes is determined. A positive result in the assay occurs when the redifferentiation of the chondrocytes is determined to be more similar to the positive control than the negative control.

The following polypeptide tested positive in this assay: PRO357.

EXAMPLE 17: Identification of PRO Polypeptides That Stimulate TNF-α Release In Human Blood (Assay 128)

This assay shows that certain PRO polypeptides of the present invention act to stimulate the release of TNF- α in human blood. PRO polypeptides testing positive in this assay are useful for, among other things, research purposes where stimulation of the release of TNF- α would be desired and for the therapeutic treatment of conditions wherein enhanced TNF- α release would be beneficial. Specifically, 200 μ 1 of human blood supplemented with 50mM Hepes buffer (plt 7.2) is aliquoted per well in a 96 well test plate. To each well is then added 300 μ 1 of either the test PRO polypeptide in 50 mM Hepes buffer (at various concentrations) or 50 mM Hepes buffer alone (negative control) and the plates are incubated at 37 °C for 6 hours. The samples are then centrifuged and 50 μ 1 of plasma is collected from each well and tested for the presence of TNF- α by ELISA assay. A positive in the assay is a higher amount of TNF- α in the PRO polypeptide treated samples as compared to the negative control samples.

The following PRO polypeptides tested positive in this assay: PRO231, PRO357, PRO725, PRO1155, PRO1306, and PRO1419.

EXAMPLE 18: Promotion of Chondrocyte Redifferentiation (Assay 129)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce the proliferation and/or redifferentiation of chondrocytes in culture. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis.

Porcine chondrocytes are isolated by overnight collagenase digestion of articular cartilage of the metacarpophalangeal joint of 4-6 month old female pigs. The isolated cells are then seeded at 25,000 cells/cm² in Ham F-12 containing 10% FBS and 4 µg/ml gentamycin. The culture media is changed every third day. On day 12, the cells are seeded in 96 well plates at 5,000 cells/well in 100µl of the same media without serum and 100 µl of either serum-free medium (negative control), staurosporin (final concentration of 5 mN; positive control).

or the test PRO polypeptide are added to give a final volume of 200 μ l/well. After 5 days at 37°C, 22 μ l of media comtaining 100μ g/ml Hoechst 33342 and 50 μ g/ml 5-CFDA is added to each well and incubated for an additional 10 minutes at 37°C. A picture of the green fluorescence is taken for each well and the differentiation state of the chondrocytes is calculated by morphometric analysis. A positive result in the assay is obtained when the >50% of the PRO polypeptide treated cells are differentiated (compared to the background obtained by the negative control).

The following PRO polypeptides tested positive in this assay: PRO229, PRO1272, and PRO4405.

EXAMPLE 19: Normal Human Dermal Fibroblast Proliferation (Assay 141)

5

10

15

20

25

35

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce proliferation of human dermal fibroblast cells in culture and, therefore, function as useful growth factors.

On day 0, human dermal fibroblast cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [fibroblast growth media (FGM, Clonetics), plus supplements: insulin, human epithelial growth factor (hEGF), gentamicin (GA-1000), and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [FGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expressed as % of the cell growth observed with control buffer.

The following PRO polypeptides stimulated normal human dermal fibroblast proliferation in this assay: PRO982, PRO357, PRO725, PRO1306, PRO1419, PRO214, PRO247, PRO337, PRO526, PRO363, PRO531, PRO1083, PRO840, PRO1080, PRO1478, PRO1134, PRO826, PRO1005, PRO809, PRO1071, PRO1411, PRO1099, PRO1025, PRO1181, PRO1126, PRO1186, PRO1192, PRO1244, PRO1274, PRO1412, PRO1286, PRO1330, PRO1347, PRO1350, PRO1373, PRO1279, PRO1340, PRO1338, PRO1343, PRO1376, PRO1387, PRO1409, PRO1474, PRO1917, PRO1760, PRO1567, PRO1887, PRO1928, PRO4341, PRO1801, PRO4333, PRO33444, PRO4322, PRO940, PRO6079, PRO6876 and PRO10096.

The following PRO polypeptides inhibited normal human dermal fibroblast proliferation in this assay: PRO181, PRO229, PRO788, PRO1194, PRO1272, PRO1488, PRO4302, PRO4408, PRO5723, PRO5725, PRO7154, and PRO7425.

30 EXAMPLE 20: Microarray Analysis to Detect Overexpression of PRO Polypeptides in Cancerous Tumors

Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of a probe from a control (normal tissue) sample, the gene or genes overexpressed in the disease tissue are identified. The implication of this result is that an overexpressed protein in a diseased tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition.

The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In the present example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in U.S. Provisional Patent Application Serial No. 60/193,767, filed on March 31, 2000 and which is herein incomported by reference.

In the present example, cancerous tumors derived from various human tissues were studied for PRO polypeptide-encoding gene expression relative to non-cancerous human tissue in an attempt to identify those PRO polypeptides which are overexpressed in cancerous tumors. Cancerous human tumor tissue from any of a variety of different human tumors was obtained and compared to a "universal" epithelial control sample which was prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung. mRNA isolated from the pooled tissues represents a mixture of expressed gene products from these different tissues. Microarray hybridization experiments using the pooled control samples generated a linear plot in a 2-color analysis. The slope of the line generated in a 2-color analysis was then used to normalize the ratios of (test:control detection) within each experiment. The normalized ratios from various experiments were then compared and used to identify clustering of gene expression. Thus, the pooled "universal control" sample not only allowed effective relative gene expression determinations in a simple 2-sample comparison, it also allowed multi-sample comparisons across several experiments.

In the present experiments, nucleic acid probes derived from the herein described PRO polypeptideencoding nucleic acid sequences were used in the creation of the microarray and RNA from a panel of nine
different tumor tissues (listed below) were used for the hybridization thereto. A value based upon the normalized
ratio-experimental ratio was designated as a "cutoff ratio". Only values that were above this cutoff ratio were
determined to be significant. Table 8 below shows the results of these experiments, demonstrating that various
PRO polypeptides of the present invention are significantly overexpressed in various human tumor tissues, as
compared to a non-cancerous human tissue control or other human tumor tissues. As described above, these data
demonstrate that the PRO polypeptides of the present invention are useful not only as diagnostic markers for the
presence of one or more cancerous tumors, but also serve as therapeutic targets for the treatment of those tumors.

TABLE 8

Molecule	is overexpressed in:	as compared to normal control:
PRO6004	colon tumor	universal normal control
PRO4981 PRO4981	colon tumor lung tumor	universal normal control universal normal control
PRO7174	colon tumor	universal normal control

		T. D. W. C	
	Molecule	TABLE 8 (cont') is overexpressed in:	as compared to normal control:
	PRO5778	lung tumor	universal normal control
	PRO5778	breast tumor	universal normal control
	PRO5778	liver tumor	universal normal control
5	1 KO5778	nver tumor	universal normal control
3	PRO4332	colon tumor	universal normal control
	PRO9799	colon tumor	universal normal control
10	PRO9909	colon tumor	universal normal control
	PRO9917	colon tumor	universal normal control
	PRO9917	lung tumor	universal normal control
	PRO9917	breast tumor	universal normal control
15			
	PRO9771	colon tumor	universal normal control
	PRO9877	colon tumor	universal normal control
20	PRO9903	colon tumor	universal normal control
	PRO9830	colon tumor	universal normal control
	PRO7155	colon tumor	universal normal control
25	PRO7155	lung tumor	universal normal control
	PRO7155	prostate tumor	universal normal control
	PRO9862	colon tumor	universal normal control
30	PRO9882	colon tumor	universal normal control
	PRO9864	colon tumor	universal normal control
35	PRO10013	colon tumor	universal normal control
	PRO9885	colon tumor	universal normal control
	PRO9879	colon tumor	universal normal control
40	PRO10111	colon tumor	universal normal control
	PRO10111	rectal tumor	universal normal control
	PRO9925	breast tumor	universal normal control
45	PRO9925	rectal tumor	universal normal control
45	PRO9925	colon tumor	universal normal control
	PRO9925	lung tumor	universal normal control
	PRO9905	colon tumor	universal normal control
50	PRO10276	colon tumor	universal normal control
	PRO9898	colon tumor	universal normal control
55	PRO9904	colon tumor	universal normal control

		TABLE 8 (cont')	
	Molecule	is overexpressed in:	as compared to normal control:
	PRO19632	colon tumor	universal normal control
	PRO19672	colon tumor	universal normal control
5			
	PRO9783	colon tumor	universal normal control
	PRO9783	lung tumor	universal normal control
	PRO9783	breast tumor	universal normal control
	PRO9783	prostate tumor	universal normal control
10	PRO9783	rectal tumor	universal normal control
	PRO10112	colon tumor	universal normal control
	PRO10284	colon tumor	universal normal control
15			
	PRO10100	colon tumor	universal normal control
		TOTAL VALUE	univolent normal control
	PRO19628	colon tumor	universal normal control
	111017000	ooion manor	mirrorom normal comitor
20	PRO19684	colon tumor	universal normal control
	111017001	TOTOL VALUE	mirroran normal control
	PRO10274	colon tumor	universal normal control
		Total Milion	dili terbili ilorinini obilitor
	PRO9907	colon tumor	universal normal control
25	110,500	oolon taatoi	universal invinial constra
	PRO9873	colon tumor	universal normal control
	110,075	ooron tantor	was reisar invitias constos
	PRO10201	colon tumor	universal normal control
			Mar viole normal volled
30	PRO10200	colon tumor	universal normal control
	PRO10196	colon tumor	universal normal control
	PRO10282	lung tumor	universal normal control
35	PRO10282	breast tumor	universal normal control
	PRO10282	colon tumor	universal normal control
	PRO10282	rectal tumor	universal normal control
	PRO19650	colon tumor	universal normal control
40			
	PRO21184	lung tumor	universal normal control
	PRO21184	breast tumor	universal normal control
	PRO21184	colon tumor	universal normal control
45	PRO21201	breast tumor	universal normal control
	PRO21201	colon tumor	universal normal control
	PRO21175	breast tumor	universal normal control
	PRO21175	colon tumor	universal normal control
50	PRO21175	lung tumor	universal normal control
	PRO21340	colon tumor	universal normal control
	PRO21340	prostate tumor	universal normal control
55	PRO21384	colon tumor	universal normal control

15

20

25

30

35

WO 02/08288 PCT/US01/21066

TABLE 8 (cont')

Molecule is overexpressed in: as compared to normal control:
PRO2.1384 lung tumor universal normal control
PRO2.1384 breast tumor universal normal control

5 EXAMPLE 21: Tumor Versus Normal Differential Tissue Expression Distribution

Oligonucleotide probes were constructed from some of the PRO polypeptide-encoding nucleotide sequences shown in the accompanying figures for use in quantitative PCR amplification reactions. The oligonucleotide probes were chosen so as to give an approximately 200-600 base pair amplified fragment from the 3' end of its associated template in a standard PCR reaction. The oligonucleotide probes were employed in standard quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in the various tumor and normal tissues tested. β-actin was used as a control to assure that equivalent amounts of nucleic acid was used in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. These assays provided the following results.

- (1) the DNA94849-2960 molecule is significantly expressed in the following tissues: cartilage, testis, colon tumor, heart, placenta, bone marrow, adrenal gland, prostate, spleen aortic endothelial cells and uterus, and not significantly expressed in the following tissues: HUVEC.
- (2) the DNA100272-2969 molecule is significantly expressed in cartilage, testis, human umbilileal vein endothelial cells (HUVEC), colon tumor, heart, placenta, bone marrow, adrenal gland, prostate, spleen and aortic endothelial cells; and not significantly expressed in uterus. Among a panel of normal and tumor cells examined, the DNA100272-2969 was found to be expressed in normal esophagus, esophageal tumor, normal stomach, the stomach tumor, normal kidney, kidney tumor, normal lung, lung tumor, normal rectum, rectal tumor, normal liver numor.
- (3) the DNA108696-2966 molecule is highly expressed in prostate and also expressed in testis, bone marrow and spleen. The DNA108696-2966 molecule is expressed in normal stomach, but not expressed in stomach tumor. The DNA108696-2966 molecule is not expressed in normal kidney, kidney tumor, normal lung, or lung tumor. The DNA108696-2966 molecule is highly expressed in normal rectum, lower expression in rectal tumor. The DNA108696-2966 molecule is not expressed in normal liver or liver tumor. The DNA108696-2966 molecule is not expressed in normal liver or liver tumor. The DNA108696-2966 molecule is not expressed in normal liver or liver tumor. The DNA108696-2966 molecule is not expressed in normal explangial tumor, cartilage, HUVEC, colon tumor, heart, placenta, adrenal gland, aortic endothelial cells and uterus.
- (4) the DNA119498-2965 molecule is significantly expressed in the following tissues: highly expressed in aortic endothelial cells, and also significantly expressed in cartilage, testis, HUVEC, colon tumor, heart, placenta, bone marrow, adrenal gaind, prostate and spicen. It is not significantly expressed in uterus.

Page 101 of 559

WO 02/08288 PCT/US01/21066

(5) the DNA119530-2968 molecule is expressed in the following tissues: normal esophagus and not expressed in the following tissues: esophageal tumors, stomach tumors, normal stomach, normal kidney, kidney tumor, normal lung, lung tumor, normal rectum, rectal tumors, normal liver or liver tumors.

- (6) the DNA129794-2967 molecule is significantly expressed in testis and adrenal gland; and not significantly expressed in cartilage, human umbilitical vein endothelial cells (HUVEC), colon tumor, heart, placenta, bone marrow, prostate, spleen, aortic endothelial cells and uterus.
- (7) the DNA131590-2962 molecule is significantly expressed in the following tissues: bone marrow, adrenal gland, prostate, spleen, uterus, cartilage, testis, colon tumor, heart, and placenta, and not significantly expressed in the following tissues: HUVEC, and aortic endothelial cells.
- (8) the DNA149995-2871 molecule is highly expressed in testis, and adrenal gland; expressed in cartilage, human umbillical vein endothelial cells (HUVEC), colon tumor, heart, prostate and uterus; weakly expressed in bone marrow, spleen and aortic endothelial cells; and not significantly expressed in placenta.
- (9) the DNA167678-2963 molecule is significantly expressed in the following tissues: normal esophagus, esophagial tumor, highly expressed in normal stomach, stomach tumor, highly expressed in normal kidney, kidney tumor, expressed in lung, lung tumor, normal rectum, rectal tumor, weakly expressed in normal liver, and not significantly expressed in liver tumor.
- (10) the DNA168028-2956 molecule is highly expressed in bone marrow; expressed in testis, human umbillical vein endothelial cells (HUVEC), colon tumor, heart, placenta, adrenal gland, prostate, spleen, aortic endothelial cells and uterus; and is weakly expressed in cartilage. Among a panel of normal and tumor samples examined, the DNA168028-2956 was found to be expressed in stomach tumor, normal kidney, kidney tumor, lung tumor, normal rectum and rectal tumor; and not expressed in normal esophagus, esophageal tumor, normal stomach, normal lung, normal liver and liver tumor.
- (11) the DNA176775-2957 molecule is highly expressed in testis; expressed in cartilage and prostate; weakly expressed in adrenal gland, spleen and uterus; and not significantly expressed in human umbilitical vein endothelial cells (HUVEC), colon tumor, heart, placenta, bone marrow and aortic endothelial cells.
- (12) the DNA177313-2982 molecule is significantly expressed in prostate and aortic endothelial cells; and not significantly expressed in cartilage, testis, human umbilical vein endothelial cells (HUVEC), colon tumor, heart, placenta, bone marrow, adrenal gland, spleen and uterus. Among a panel of normal and tumor cells, the DNA177313-2982 molecule was found to be expressed in esophageal tumor but not in normal esophagus, normal stomach, stomach tumor, normal kidney, kidney tumor, normal lung, lung tumor, normal rectum, rectal tumor,
- 30 normal liver and liver tumor.

WCG268268 (IB#7/E-AVO6206236 opc.)

5

10

15

20

25

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

WHAT IS CLAIMED IS:

1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEO ID NO:14), Figure 16 (SEO ID NO:16). Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEO ID NO:92). Figure 94 (SEQ ID NO:94), Figure 96 (SEO ID NO:96), Figure 98 (SEO ID NO:98), Figure 100 (SEO ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEO ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEO ID NO:172), Figure 174 (SEO ID NO:174), Figure 176 (SEO ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEO ID NO:196), Figure 198 (SEO ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), and Figure 244 (SEQ ID NO:244).

10

15

20

25

30

35

WO 02/08288 PCT/US01/21066

- 2. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in Figures 1A-1B (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figures 59A-59B (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEO ID NO:69), Figure 71 (SEO ID NO:71), Figure 73 (SEQ ID NO:73), Figure 75 (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEO ID NO:93). Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121). Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEO ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEO ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165), Figure 167 (SEQ ID NO:167), Figure 169 (SEQ ID NO:169), Figure 171 (SEQ ID NO:171), Figure 173 (SEQ ID NO:173), Figure 175 (SEQ ID NO:175), Figure 177 (SEQ ID NO:177), Figure 179 (SEQ ID NO:179), Figure 181 (SEQ ID NO:181), Figure 183 (SEQ ID NO:183), Figure 185 (SEQ ID NO:185), Figure 187 (SEQ ID NO:187), Figure 189 (SEQ ID NO:189), Figure 191 (SEQ ID NO:191), Figure 193 (SEQ ID NO:193), Figure 195 (SEQ ID NO:195), Figure 197 (SEQ ID NO:197), Figure 199 (SEQ ID NO:199), Figure 201 (SEQ ID NO:201), Figure 203 (SEQ ID NO:203), Figure 205 (SEO ID NO:205), Figure 207 (SEQ ID NO:207), Figure 209 (SEQ ID NO:209), Figure 211 (SEQ ID NO:211), Figure 213 (SEQ ID NO:213), Figure 215 (SEQ ID NO:215), Figure 217 (SEQ ID NO:217), Figure 219 (SEQ ID NO:219), Figure 221 (SEQ ID NO:221), Figure 223 (SEQ ID NO:223), Figure 225 (SEQ ID NO:225), Figure 227 (SEO ID NO:227), Figure 229 (SEQ ID NO:229), Figure 231 (SEQ ID NO:231), Figure 233 (SEQ ID NO:233), Figure 235 (SEQ ID NO:235), Figure 237 (SEQ ID NO:237), Figure 239 (SEQ ID NO:239), Figure 241 (SEQ ID NO:241), and Figure 243 (SEO ID NO:243).
 - 3. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence

5

10

15

20

25

30

35

selected from the group consisting of the full-length coding sequence of the nucleotide sequence shown in Figures 1A-1B (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEO ID NO:55), Figure 57 (SEO ID NO:57), Figures 59A-59B (SEO ID NO:59), Figure 61 (SEO ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figure 75 (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEO ID NO:157), Figure 159 (SEO ID NO:159), Figure 161 (SEO ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165), Figure 167 (SEQ ID NO:167), Figure 169 (SEQ ID NO:169), Figure 171 (SEQ ID NO:171), Figure 173 (SEQ ID NO:173), Figure 175 (SEQ ID NO:175), Figure 177 (SEQ ID NO:177), Figure 179 (SEQ ID NO:179), Figure 181 (SEQ ID NO:181), Figure 183 (SEQ ID NO:183), Figure 185 (SEO ID NO:185), Figure 187 (SEO ID NO:187), Figure 189 (SEO ID NO:189), Figure 191 (SEQ ID NO:191), Figure 193 (SEQ ID NO:193), Figure 195 (SEQ ID NO:195), Figure 197 (SEQ ID NO:197), Figure 199 (SEQ ID NO:199), Figure 201 (SEQ ID NO:201), Figure 203 (SEQ ID NO:203), Figure 205 (SEQ ID NO:205), Figure 207 (SEQ ID NO:207), Figure 209 (SEQ ID NO:209), Figure 211 (SEQ ID NO:211), Figure 213 (SEQ ID NO:213), Figure 215 (SEQ ID NO:215), Figure 217 (SEQ ID NO:217), Figure 219 (SEQ ID NO:219), Figure 221 (SEQ ID NO:221), Figure 223 (SEQ ID NO:223), Figure 225 (SEQ ID NO:225), Figure 227 (SEQ ID NO:227), Figure 229 (SEQ ID NO:229), Figure 231 (SEQ ID NO:231), Figure 233 (SEQ ID NO:233), Figure 235 (SEQ ID NO:235), Figure 237 (SEQ ID NO:237), Figure 239 (SEQ ID NO:239), Figure 241 (SEQ ID NO:241), and Figure 243 (SEQ ID NO:243).

 Isolated nucleic acid having at least 80% nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

10

15

20

25

30

35

WO 02/08288

PCT/US01/21066

Page 105 of 359

- A vector comprising the nucleic acid of Claim 1.
- A host cell comprising the vector of Claim 5.
- The host cell of Claim 6, wherein said cell is a CHO cell.
- 8. The host cell of Claim 6, wherein said cell is an E. coli.
- 9. The host cell of Claim 6, wherein said cell is a yeast cell.
- 10. A process for producing a PRO polypeptide comprising culturing the host cell of Claim 6 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.
- An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid 11. sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEO ID NO:52), Figure 54 (SEO ID NO:54), Figure 56 (SEO ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEO ID NO:84), Figure 86 (SEO ID NO:86). Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure

10

25

30

35

WO 02/08288

PCT/US01/21066

Page 106 of 359

166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:185), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 206 (SEQ ID NO:195), Figure 207 (SEQ ID NO:196), Figure 208 (SEQ ID NO:208), Figure 208 (SEQ ID NO:207), Figure 208 (SEQ ID NO:208), Figure 208 (SEQ ID NO:208), Figure 208 (SEQ ID NO:208), Figure 208 (SEQ ID NO:216), Figure 208 (SEQ ID NO:216), Figure 208 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 209 (SEQ ID NO:220), Figure 222 (SEQ ID NO:226), Figure 226 (SEQ ID NO:226), Figure 227 (SEQ ID NO:226), Figure 228 (SEQ ID NO:227), Figure 230 (SEQ ID NO:236), Figure 230 (SEQ ID NO:236), Figure 231 (SEQ ID NO:236), Figure 234 (SEQ ID NO:237), Figure 244 (SEQ ID NO:244),

- An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under any ATCC accession number
 shown in Table 7.
 - A chimeric molecule comprising a polypeptide according to Claim 11 fused to a heterologous amino acid sequence.
- 20 14. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is an epitope tag sequence.
 - The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.
 - An antibody which specifically binds to a polypeptide according to Claim 11.
 - 17. The antibody of Claim 16, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.
 - 18. Isolated nucleic acid having at least 80% nucleic acid sequence identity to:
 - (a) a nucleotide sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 25 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:34), Figure 30 (SEQ ID NO:34)

WCq098088 (He ///E NVO9208288 qpc) Page (67 of 55)

WO 02/08288 PCT/US01/21066

5

10

15

20

25

30

35

ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEO ID NO:104), Figure 106 (SEO ID NO:106), Figure 108 (SEO ID NO:108), Figure 110 (SEO ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEO ID NO:126), Figure 128 (SEO ID NO:128), Figure 130 (SEO ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEO ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), or Figure 244 (SEQ ID NO:244), lacking its associated signal peptide;

(b) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:14), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:26), Figure 28 (SEQ ID NO:30), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:44), Figure 36 (SEQ ID NO:48), Figure 40 (SEQ ID NO:49), Figure 50 (SEQ ID NO:59), Figure 50 (SED ID NO:59), Figure 50 (SED

WC000808 Bits WF-W0000838 opc] Fags 108 ot 350

PCT/US01/21066

WO 02/08288

5

10

15

20

25

30

35

64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEO ID NO:72), Figure 74 (SEO ID NO:74), Figure 76 (SEO ID NO:76), Figure 78 (SEO ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO: 108), Figure 110 (SEQ ID NO: 110), Figure 112 (SEQ ID NO: 112), Figure 114 (SEQ ID NO: 114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEO ID NO:124), Figure 126 (SEO ID NO:126), Figure 128 (SEO ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEO ID NO:172), Figure 174 (SEO ID NO:174), Figure 176 (SEO ID NO:176), Figure 178 (SEO ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEO ID NO:208), Figure 210 (SEO ID NO:210), Figure 212 (SEO ID NO:212), Figure 214 (SEO ID NO:214), Figure 216 (SEO ID NO:216), Figure 218 (SEO ID NO:218), Figure 220 (SEO ID NO:220), Figure 222 (SEO ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), or Figure 244 (SEQ ID NO:244), with its associated signal peptide; or

(c) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:10), Figure 12 (SEQ ID NO:110), Figure 12 (SEQ ID NO:10), Figure 13 (SEQ ID NO:10), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:24), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:25), Figure 28 (SEQ ID NO:24), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:36), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:40), Figure 45 (SEQ ID NO:45), Figure 46 (SEQ ID NO:40), Figure 50 (SEQ ID NO:50), Figure 50 (SEQ I

5

10

15

20

25

30

35

ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEO ID NO:144), Figure 146 (SEO ID NO:146), Figure 148 (SEO ID NO:148), Figure 150 (SEO ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEO ID NO:172), Figure 174 (SEO ID NO:174), Figure 176 (SEO ID NO:176), Figure 178 (SEO ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEO ID NO:200), Figure 202 (SEO ID NO:202), Figure 204 (SEO ID NO:204), Figure 206 (SEO ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEO ID NO:236), Figure 238 (SEO ID NO:238), Figure 240 (SEO ID NO:240), Figure 242 (SEO ID NO:242), or Figure 244 (SEO ID NO:244), lacking its associated signal peptide.

19. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) an amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 23 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 56 (SEQ ID NO:55), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:50), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 56 (SEQ ID NO:56

5

10

15

20

25

30

35

ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEO ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEO ID NO:178), Figure 180 (SEO ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEO ID NO:204), Figure 206 (SEO ID NO:206), Figure 208 (SEO ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEO ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), or Figure 244 (SEQ ID NO:244), lacking its associated signal peptide:

an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEO ID NO:26), Figure 28 (SEO ID NO:28), Figure 30 (SEO ID NO:30), Figure 32 (SEO ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108). Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEO ID NO:114), Figure 116 (SEO

PCT/US01/21066

WO 02/08288

5

10

15

20

25

30

35

ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEO ID NO:124), Figure 126 (SEO ID NO:126), Figure 128 (SEO ID NO:128), Figure 130 (SEO ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEO ID NO:146), Figure 148 (SEO ID NO:148), Figure 150 (SEO ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEO ID NO:166), Figure 168 (SEO ID NO:168), Figure 170 (SEO ID NO:170), Figure 172 (SEO ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEO ID NO:188), Figure 190 (SEO ID NO:190), Figure 192 (SEO ID NO:192), Figure 194 (SEO ID NO:194), Figure 196 (SEO ID NO:196), Figure 198 (SEO ID NO:198), Figure 200 (SEO ID NO:200), Figure 202 (SEO ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEO ID NO:222), Figure 224 (SEO ID NO:224), Figure 226 (SEO ID NO:226), Figure 228 (SEO ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), or Figure 244 (SEQ ID NO:244), with its associated signal peptide; or

an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEO ID NO:2), Figure 4 (SEO ID NO:4), Figure 6 (SEO ID NO:6), Figure 8 (SEO ID NO:8), Figure 10 (SEO ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEO ID NO:42), Figure 44 (SEO ID NO:44), Figure 46 (SEO ID NO:46), Figure 48 (SEO ID NO:48), Figure 50 (SEO ID NO:50), Figure 52 (SEO ID NO:52), Figure 54 (SEO ID NO:54), Figure 56 (SEO ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEO ID NO:80), Figure 82 (SEO ID NO:82), Figure 84 (SEO ID NO:84), Figure 86 (SEO ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEO ID NO:102), Figure 104 (SEO ID NO:104), Figure 106 (SEO ID NO:106), Figure 108 (SEO ID NO:108). Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEO ID NO:124), Figure 126 (SEO ID NO:126), Figure 128 (SEO ID NO:128), Figure 130 (SEO ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure

5

10

15

20

30

35

WO 02/08288 PCT/US01/21066

138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEO ID NO:170), Figure 172 (SEO ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEO ID NO:194), Figure 196 (SEO ID NO:196), Figure 198 (SEO ID NO:198), Figure 200 (SEO ID NO:200), Figure 202 (SEO ID NO:202), Figure 204 (SEO ID NO:204), Figure 206 (SEO ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEO ID NO:222), Figure 224 (SEO ID NO:224), Figure 226 (SEO ID NO:226), Figure 228 (SEO ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), or Figure 244 (SEQ ID NO:244), lacking its associated signal peptide.

- 20. A method for stimulating the proliferation of or gene expression in pericyte cells, said method comprising contacting said cells with a PRO982, PRO1160, PRO1187, or PRO1329 polypeptide, wherein the proliferation of or gene expression in said cells is stimulated.
- 21. A method for stimulating the proliferation or differentiation of chondrocyte cells, said method comprising contacting said cells with a PRO357, PRO229, PRO1272 or PRO4405 polypeptide, wherein the proliferation or differentiation of said cells is stimulated.
- 25 22. A method for stimulating the release of TNF-α from human blood, said method comprising contacting said blood with a PRO231, PRO357, PRO725, PRO1155, PRO1306 or PRO1419 polypeptide, wherein the release of TNF-α from said blood is stimulated.
 - 23. A method for stimulating the proliferation of normal human dermal fibroblast cells, said method comprising contacting said cells with a PRO982, PRO357, PRO725, PRO1306, PRO1419, PRO214, PRO247, PRO337, PRO526, PRO363, PRO531, PRO1083, PRO840, PRO1080, PRO1478, PRO1134, PRO826, PRO1005, PRO809, PRO1071, PRO1411, PRO1309, PRO1025, PRO1181, PRO1126, PRO1186, PRO1192, PRO1244, PRO1412, PRO1286, PRO1330, PRO1347, PRO1305, PRO1273, PRO1279, PRO1340, PRO1338, PRO1343, PRO1376, PRO1387, PRO1409, PRO1474, PRO1417, PRO1760, PRO187, PRO1928, PRO4341, PRO1801, PRO4333, PRO3543, PRO3444, PRO4322, PRO9940, PRO6079, PRO9836 or PRO10096 polypeptide, wherein the proliferation of said cells is stimulated.

Page 113 of 359

PCT/US01/21066

WCG268268 (IB#7/E-AV-06206236 opc.)

WO 02/08288

24. A method for inhibiting the proliferation of normal human dermal fibroblast cells, said method comprising contacting said cells with a PRO181, PRO229, PRO788, PRO1194, PRO1272, PRO1488, PRO4408, PRO5723, PRO5725, PRO7154, and PRO7425 polypeptide, wherein the proliferation of said cells is inhibited.

5 25. A method for detecting the presence of tumor in an mammal, said method comprising comparing the level of expression of any PRO polypeptide shown in Table 8 in (a) a test sample of cells taken from said mammal and (b) a control sample of normal cells of the same cell type, wherein a higher level of expression of said PRO polypeptide in the test sample as compared to the control sample is indicative of the presence of tumor in said mammal.

10
26. The method of Claim 25, wherein said tumor is lung tumor, colon tumor, breast tumor, prostate tumor, rectal tumor, or liver tumor.

27. An oligonucleotide probe derived from any of the nucleotide sequences shown in the 15 accompanying figures.

Page 114 of 359

1/246

WC0268268 [Be://E_W/06206286 opc]

FIGURE 1A

GCAGCCCTAGCAGGGATGACATGATGCTGTTGGTGCAGGGTGCTTGTTGCTCGAACCAGTG GCTGGCGGCGGTGCTCCTCAGCCTGTGCTGCCTGCTACCCTCCTGCCTCCCGGCTGGACAGA GTGTGGACTTCCCCTGGGCGGCCGTGGACAACATGATGGTCAGAAAAGGGGACACGGCGGTG CTTAGGTGTTATTTGGAAGATGGAGCTTCAAAGGGTGCCTGGCTGAACCGGTCAAGTATTAT TTTTGCGGGAGGTGATAAGTGGTCAGTGGATCCTCGAGTTTCAATTTCAACATTGAATAAAA GGGACTACAGCCTCCAGATACAGAATGTAGATGTGACAGATGATGGCCCATACACGTGTTCT GTTCAGACTCAACATACACCCAGAACAATGCAGGTGCATCTAACTGTGCAAGTTCCTCCTAA GATATATGACATCTCAAATGATATGACCGTCAATGAAGGAACCAACGTCACTCTTACTTGTT TGGCCACTGGGAAACCAGAGCCTTCCATTTCTTGGCGACACATCTCCCCATCAGCAAAACCA TTTGAAAATGGACAATATTTGGACATTTATGGAATTACAAGGGACCAGGCTGGGGAATATGA ATGCAGTGCGGAAAATGATGTGTCATTCCCAGATGTGAGGAAAGTAAAAGTTGTTGTCAACT TTGCTCCTACTATTCAGGAAATTAAATCTGGCACCGTGACCCCCGGACGCAGTGGCCTGATA AGATGTGAAGGTGCAGGTGTGCCGCCTCCAGCCTTTGAATGGTACAAAGGAGAGAAGAAGCT CTTCAATGGCCAACAAGGAATTATTATTCAAAATTTTAGCACAAGATCCATTCTCACTGTTA CCAACGTGACACGGGGCACTTCGGCAATTATACTTGTGTGGCTGCCAACAAGCTAGGCACA ACCAATGCGAGCCTGCCTCTTAACCCTCCAAGTACAGCCCAGTATGGAATTACCGGGAGCGC TGATGTTCTTCTCCTGCTGGTACCTTGTGTTGACACTGTCCTCTTTCACCAGCATATTCT ACCTGAAGAATGCCATTCTACAATAAATTCAAAGACCCATAAAAGGCTTTTAAGGATTCTCT GAAAGTGCTGATGGCTGGATCCAATCTGGTACAGTTTGTTAAAAGCAGCGTGGGATATAATC AGCAGTGCTTACATGGGGATGATCGCCTTCTGTAGAATTGCTCATTATGTAAATACTTTAAT TCTACTCTTTTTTGATTAGCTACATTACCTTGTGAAGCAGTACACATTGTCCTTTTTTTAAG ACGTGAAAGCTCTGAAATTACTTTTAGAGGATATTAATTGTGATTTCATGTTTGTAATCTAC AACTTTTCAAAAGCATTCAGTCATGGTCTGCTAGGTTGCAGGCTGTAGTTTACAAAAACGAA TATTGCAGTGAATATGTGATTCTTTAAGGCTGCAATACAAGCATTCAGTTCCCTGTTTCAAT TTGCCTTCAGATTATTTCTTCAAAATATAACACATATCTAGATTTTTCTGCTCGCATGATAT TCAGGTTTCAGGAATGAGCCTTGTAATATAACTGGCTGTGCAGCTCTGCTTCTCTTTCCTGT AAGTTCAGCATGGGTGTGCCTTCATACAATAATATTTTTCTCTTTGTCTCCAACTAATATAA AATGTTTTGCTAAATCTTACAATTTGAAAGTAAAAATAAACCAGAGTGATCAAGTTAAACCA TACACTATCTCTAAGTAACGAAGGAGCTATTGGACTGTAAAAATCTCTTCCTGCACTGACAA TGGGGTTTGAGAATTTTGCCCCACACTAACTCAGTTCTTGTGATGAGAGACAATTTAATAAC AGTATAGTAAATATACCATATGATTTCTTTAGTTGTAGCTAAATGTTAGATCCACCGTGGGA AATCATTCCCTTTAAAATGACAGCACAGTCCACTCAAAGGATTGCCTAGCAATACAGCATCT TTTCCTTTCACTAGTCCAAGCCAAAAATTTTAAGATGATTTGTCAGAAAGGGCACAAAGTCC TATCACCTAATATTACAAGAGTTGGTAAGCGCTCATCATTAATTTTATTTTGTGGCAGCTAA GTTAGTATGA CAGAGGCAGTGCTCCTGTGGACAGGAGCATTTTGCATATTTTCCATCTGAAA GTATCACTCAGTTGATAGTCTGGAATGCATGTTATATATTTTAAAACTTCCAAAATATATTA TAACAAACATTCTATATCGGTATGTAGCAGACCAATCTCTAAAATAGCTAATTCTTCAATAA AATCTTTCTATATAGCCATTTCAGTGCAAACAAGTAAAATCAAAAAAGACCATCCTTTATTT TTCCTTACATGATATGTAAGATGCGATCAAATAAAGACAAAACACCAGTGATGAGAATAT CTTAAGATAAGTAATTATCAAATTATTGTGAATGTTAAATTATTTCTACTATAAAGAAGCAA AACTACATTTTTGAAGGAAAATGCTGTTACTCTAACATTAATTTACAGGAATAGTTTGATGG TTTCACTCTTTACTAAAGAAAGGCCATCACCTTGAAAGCCATTTTACAGGTTTGATGAAGTT ACCAATTTCAGTACACCTAAATTTCTACAAATAGTCCCCTTTTACAAGTTGTAACAACAAAG ACCCTATAATAAAATTAGATACAAGAAATTTTGCAGTGGTTATACATATTTGAGATATCTAG CCCAAAGTACATCATAAATCAATTTTAATTAGAAAAATGAATCTTAAATGAGGGGACATAAG TATACTCTTTCCACAAAATGGCAATAATAAGGCATAAAGCTAGTAAATCTACTAACTGTAAT AAATGTATGACATTATTTTGATTGATACATTAAAAAAGAGTTTTTAGAACAAATATGGCATT TAACTTTATTATTTGCTTTTAAGAAATATTCTTTGTGGAATTGTTGAATAAACTATAA AATATTATTTTGTATTGCAGCTTTAAAGTGGCACACTCCATAATAATCTACTACTAGAAAT

WC6268368 [Her//E/W/06266286 opc]

WO 02/08288 PCT/US01/21066

Page 115 of 359

2/246

FIGURE 1B

AAGAATGCATATTATTCAGTGACCGCTTTCCTAGAGTTAAAATACCTCCTCTTTGTAAGGTT TGTAGGTAAATTGAGGTATAAACTATGGATGAACCAAATAATTAGTTCAAAGTGTTGTCATG ATTCCAAATTTGTGGAGTCTGGTGTTTTTACCATAGAATGTGACAGAAGTACAGTCATAGCT CAGTAGCTATATGTATTTGCCTTTATGTTAGAAGAGACTTTCTTGAGTGACATTTTTAAATA GAGGAGGTATTCACTATGTTTTTCTGTATCACAGCAGCATTCCTAGTCCTTAGGCCCTCGGA CAGAGTGAAATCATGAGTATTTATGAGTTCAATATTGTCAAATAAGGCTACAGTATTTGCTT TTTTGTGTGAATGTATTGCATATAATGTTCAAGTAGATGATTTTACATTTATGGACATATAA AATGTCTGATTACCCCATTTTATCAGTCCTGACTGTACAAGATTGTTGCAATTTCAGAATAG CAGTTTTATAAATTGATTTATCTTTTAATCTATAACAATTTGTGTTAGCTGTTCATTTCAGG AAGGAAGAAAAATAAGTAGCAGTTTAAAAATGAGAATGGAGAGAAAAGAAAAGAATG AAAAGGAAAGGCAGTAAAGAGGGAAAAAAAAGGAAGGATGAAGGAATGAAGGAAGGAAGGA GTAGTTAACTTACACATTTGCATTCTTAGTTTAACTGCAAGTGGTGTAACTATGTTTTTCAA TGATCGCATTTGAAACATAAGTCCTATTATACCATTAAGTTCCTATTATGCAGCAATTATAT AATAAAAGTACTGCCCAAGTTATAGTAATGTGGGTGTTTTTGAGACACTAAAAGATTTGAG AGGGAGAATTTCAAACTTAAAGCCACTTTTGGGGGGTTTATAACTTAACTGAAAAATTAATG CTTCATCATAACATTTAAGCTATATCTAGAAAGTAGACTGGAGAACTGAGAAAATTACCCAG GTAATTCAGGGAAAAAAAAAAATATATATATATAAATACCCCTACATTTGAAGTCAGAAA ACTCTGAAAAACTGAATTATCAAAGTCAATCATCTATAATGATCAAATTTACTGAACAATTG TTAATTTATCCATTGTGCTTAGCTTTGTGACACAGCCAAAAGTTACCTATTTAATCTTTTCA ATAAAAATTGTTTTTTGAAATCCAGAAATGATTTAAAAAGAGGTCAGGTTTTTAACTATTTÁ TTGAAGTATGTGGATGTACAGTATTTCAATAGATATGAATATGAATAAATGGTATGCCTTAA GATTCTTTGAATATGTATTTACTTTAAAGACTGGAAAAAGCTCTTCCTGTCTTTTAGTAAAA CATCCATATTTCATAACCTGATGTAAAATATGTTGTACTGTTTCCAATAGGTGAATATAAAC

Page 116 of 359

WO 02/08288 PCT/US01/21066

3/246

FIGURE 2

></usr/seqdb2/sst/DNA/Dnaseqs.full/ss.DNA92259

><subunit 1 of 1, 354 aa, 1 stop

><MW: 38719, pI: 6.12, NX(S/T): 6

MDMMLLVQCACCSNQWLAAVLLSLCCLLPSCLPAGQSVDFPWAAVDNMWVRKGDTAVLRCYL EDGASKGAWLNRSSIIFAGGDKWSVDPRVSISTLNKRDYSLQIQNVDVTDDGFYTCSVQTQH TRETMGVHLTVQVPPKIYDISNDMTVNEGENVPLICLAFGKEPSISWRHISFSAKFPERGO YLDIYGITEDQAGEYECSAENDVSFPDVRKVKVVVNFAPIJGEIKSGTVTPGRSGLIRCEGA GVPPPAFEWYKGEKKLFNGQQGIIJQNFSTRSILTVTTUVTQBHFGNYTCVAANKLGTTNASL PLNPPSTAQYGITGSADVLFSCWYLVLTLSSFTSIFYLKNAILO

Important features of the protein:

Signal peptide:

WO0268268 [He://E-/W/00206286 opc]

amino acids 1-33

Transmembrane domain:

amino acids 322-343

N-glycosylation sites.

amino acids 73-77, 155-159, 275-279, 286-290, 294-298, 307-311

Tyrosine kinase phosphorylation site.

amino acids 180-188

N-myristoylation sites.

amino acids 9-15, 65-71, 69-75, 153-159, 241-247, 293-299, 304-310, 321-327

Myelin P0 protein.

amino acids 94-123

Page 117 of 359

4/246

WC0268268 [Be://E_W/06206286 opc]

FIGURE 3

GACGGCGGCGCGCGCGCGCGCAGCTATTGCTGGACGCCAGTGGGAGAGCGAGGCCTGAG CCTCTGCGTCTAGGATCAAA**TG**GTTTCAATCCCAGAATACTATGAAGGCAAGAACGTCCTC CTCACAGGAGCTACCGGTTTTCTAGGGAAGGTGCTTCTGGAAAAGTTGCTGAGGTCTTGTCC TGGAAGAGTCCTTAGTGGCAAGCTTTTTGACAGATTGAGAGATGAAAATCCAGATTTTAGA GAGAAAATTATAGCAATCAACAGCGAACTCACCCAACCTAAACTGGCTCTCAGTGAAGAAGA TAAAGAGGTGATCATAGATTCTACCAATATTATATTCCACTGTGCAGCTACAGTAAGGTTTA ATGAAAATTTAAGAGATGCTGTTCAGTTAAATGTGATTGCAACGCGACAGCTTATTCTCCTT GCACAACAAATGAAGAATCTGGAAGTGTTCATGCATGTATCAACAGCATATGCCTACTGTAA TAATACATACATATACACAAAAGCATTGGCAGAATATGTTGTACAACAAGAAGGAGCAAAAC TAAATGTGGCAATTGTAAGGCCATCGATTGTTGGTGCCAGTTGGAAAGAACCTTTTCCAGGA TGGATTGATAACTTTAATGGACCAAGTGGTCTCTTTATTGCGGCAGGGAAAGGAATTCTTCG AACAATACGTGCCTCCAACAATGCCCTTGCAGATCTTGTTCCTGTAGATGTAGTTGTCAACA TGAGTCTTGCGGCAGCCTGGTATTCCGGAGTTAATAGACCAAGAAACATCATGGTGTATAAT TGTACAACAGGCAGCACTAATCCTTTCCACTGGGGTGAAGTTGAGTACCATGTAATTTCCAC TTTCAAGAGGAATCCTCTCGAACAGGCCTTCAGACGGCCCAATGTAAATCTAACCTCCAATC ATCTTTTATATCATTACTGGATTGCTGTAAGCCATAAGGCCCCAGCATTCCTGTATGATATC TACCTCAGGATGACTGGAAGAAGCCCAAGGATGATGAAAACAATAACTCGTCTTCACAAAGC TATGGTGTTTCTTGAATATTTCACAAGTAATTCTTGGGTTTGGAATACTGAGAATGTCAATA TGTTAATGAATCAACTAAACCCTGAAGATAAAAAGACCTTCAATATTGATGTACGGCAGTTA AATGTCTGGCCTCCCTGCAGCCAGAAAACATCTGAACAAGTTGCGGAATATACGTTATGGTT TTAATACTATCCTTGTGATCCTCATCTGGCGCATTTTTATTGCAAGATCACAAATGGCAAGA AATATCTGGTACTTTGTGGTTAGTCTGTGTTACAAGTTTTTGTCATACTTCCGAGCATCCAG CACTATGAGATACTGAAGACCAAGGATTCAGCATTAGAACATCTATACATATGGTGATCTAA ATGTACAAAATGTAAAATGTATAAGTCATCTCACTTTTTGTCAAGACATTAAACCATCTTAG ATCGGAGTGTGAAGTAAATTATGGTATATTTTATGTAACATTTTAATGTTTATGCTCATAAA ACTTAGTGAACACACTGTGTTATGCCAGCTCAAATCTACAGTAGCCACCAAAACCATGACTT AATATTTTGAGCCCTAGAAGAAGGGGTGTGCTGAGGACAAGAGTGGGGAAATAGGAACACT GACCAGTATAACTGTGCAATTCTGGAACATATTAATTAAAATAATATGCCTTAACATATAGT GTTGGTAGATATTTGATTCTTCATTTTTTTTTTTTTCATTAGTTGAAGTGGGTTTTAGTTT TGTTTAAAATTATAACCAGCGTATTTTCACATCATTCTGTAAGTTAAATGATATCAAACATG AAAGAGAT GTTCTCATTTTTCTTTTTCTGATTAAACGTCTGATGCATATCATTTTTCTATAA GTAATCAGTTGCTTTTAAAATCAGAAGGCTATATTATTCTAATGACCCTATTCGATCTAAAT GGGTTTGAGAATCCATATCAGCAACATACGTGTTTTTTGACAGAAAGTGAAAACAAATTCCG TAAAACTGTTAGTATCAAAAAGAATAGGAATACAGTTTTCTTTTCCACATTATGATCAAATAAA AATCTTGTGAGATTGTTAAAAA

Page 118 of 359

5/246

FIGURE 4

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA94849

><subunit 1 of 1, 515 aa, 1 stop

><MW: 59357, pI: 9.40, NX(S/T): 3

MVSIPEYYEGKNVLLTGATGFLGKVLLEKLLRSCPKVNSVYVLVRQKAGQTPQERVEEVL SGKLFDRLRDENPDFREKIIAINSELTOPKLALSEEDKEVIIDSTNIIFHCAATVRFNEN LRDAVQLNVIATROLILLAQOMKNLEVFMHVSTAYAYCNRKHIDEVVYPPPVDPKKLIDS LEWMDDGLVNDITPKLIGDRPNTYIYTKALAEYVVOOEGAKLNVAIVRPSIVGASWKEPF PGWIDNFNGPSGLFIAAGKGILRTIRASNNALADLVPVDVVVNMSLAAAWYSGVNRPRNI MVYNCTTGSTNPFHWGEVEYHVISTFKRNPLEQAFRRPNVNLTSNHLLYHYWIAVSHKAP AFLYDIYLRMTGRSPRMMKTITRLHKAMVFLEYFTSNSWVWNTENVNMLMNQLNPEDKKT FNIDVRQLHWAEYIENYCLGTKKYVLNEEMSGLPAARKHLNKLRNIRYGFNTILVILIWR IFIARSOMARNIWYFVVSLCYKFLSYFRASSTMRY

Important features of the protein: Transmembrane domain:

Amino acids

WC0268268 [Be://E-W/00206286 opc]

469-488

N-glycosylation sites:

Amino acids

283-287;304-308;341-345

Tyrosine kinase phosphorylation site:

Amino acids

160-169

N-myristoylation sites:

Amino acids 219-225;252-258;260-266;452-458

Leucine zipper pattern: 439-461

Amino acids

Page 119 of 359

6/246

WC0268268 [Be://E_W/06206286 opc]

FIGURE 5

CGATGCCGGCGGTCAGTGGTCCAGGTCCCTTATTCTGCCTTCTCCTCCTGCTCCTGGACCCCCACAGCCCTGAGACGGGTGTCCTCCTCTACGCAGGTTTGAGTACAAGCTCAGCTTCAAAGG CCCAAGGCTGGCATTGCCTGGGGCTGGAATACCCTTCTGGAGCCATCATGGAGACGCCATCC TGGGCCTGGAGGAAGTGCGGCTGACGCCATCCATGAGGAACCGGAGTGGCGCCGTGTGGAGC AGGGCCTCTGTCCCCTTCTCTGCCTGGGAAGTAGAGGTGCAGATGAGGGTGACGGGACTGGG GCGCCGGGGAGCCCAGGGCATGGCCGTGTGGTACACCCGGGGCAGGGGCCATGTAGGCTCTG TCCTTGGGGGGCTGGCTTCGTGGGACGGCATCGGGATCTTCTTTGACTCTCCGGCAGAGGAT ACTCAGGACAGTCCTGCCATCCGTGTGCTGGCCAGCGACGGGCACATCCCCTCTGAGCAGCC TGGGGATGGAGCTAGCCAAGGGCTGGGCTCCTGTCATTGGGACTTCCGGAACCGGCCACACT CCTTCAGAGCACGGATCACCTACTGGGGGCAGAGGCTGCGCATGTCCTTGAACAGTGGCCTC ACTCCCAGTGATCCAGGTGAGTTCTGTGTGGGTGGGGGCCCCTGCTTTTGGTCCCTGGAGG TTTCTTTGGGGTCTCAGCAGCCACCGGCACCCTGGCAGGTGAGGATCCCACTGGACAGGTTC CCCCTCAGCCCTTCCTGGAGATGCAGCAGCTCCGCCTGGCGAGGCAGCTGGAAGGGCTGTGG GCAAGGCTGGGCTTGGGCACCAGGGAGGATGTAACTCCAAAATCAGACTCTGAAGCTCAAGG AGAAGGGGAAAGGCTCTTTGACCTGGAGGAGACGCTGGGCAGACACCGCCGGATCCTGCAGG CTCTGCGGGGTCTCTCCAAGCAGCTGGCCCAGGCTGAGAGACAATGGAAGAAGCAGCTGGGG CCCCCAGGCCAAGCCAGGCCTGACGGAGGCTGGGCCCTGGATGCTTCCTGCCAGATTCCATC CACCCCAGGGAGGGGTGGCCACCTCTCCATGTCACTCAATAAGGACTCTGCCAAGGTCGGTG CCCTGCTCCATGGACAGTGGACTCTGCTCCAGGCCCTGCAAGAGATGAGGGATGCAGCTGTC CGCATGGCTGCAGAAGCCCAGGTCTCCTACCTGCCTGTGGGCATTGAGCATCATTTCTTAGA GCTGGACCACATCCTGGGCCTCCTGCAGGAGGAGCTTCGGGGCCCGGCGAAGGCAGCCA AGGCCCCCGCCACCTGGCCAGCCCCAAGGGCCTCCTCGTGCCTGCAGCCTGCATCTTC GAACAAGAGCCTTCAGGAGTGTCTGTCCACAGGCAGCCTTCCTCTGGGTCCTGCACCACACA TATCCTCTCCGTCTGGGTGCCCAGCTCCCACGCACACCTGAGCTTTCGGCATGCTCCCACCT AAAAAAAAAAAAAAAAAAAAAAA

Page 130 of 359

7/246

FIGURE 6

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA96883

><subunit 1 of 1, 514 aa, 1 stop ><MW: 55687, pI: 8.78, NX(S/T): 2

MPAVSGPGPLFCLLLLLDPHSPETGCPPLRRFEYKLSFKGPRLALPGAGIPFWSHHGDA ILGLEEVRLTPSMRNRSGAVWSRASVPFSAWEVEVQMRVTGLGRRGAQGMAVWYTRGRGH VGSVLGGLASWDGIGIFFDSPAEDTQDSPAIRVLASDGHIPSEQPGDGASQGLGSCHWDF RNRPHSFRARITYWGORLRMSLNSGLTPSDPGEFCVDVGPLLLVPGGFFGVSAATGTLAG EDPTGQVPPQPFLEMQQLRLARQLEGLWARLGLGTREDVTPKSDSEAQGEGERLFDLEET LGRHRRILOALRGLSKOLAOAEROWKKOLGPPGOARPDGGWALDASCOIPSTPGRGGHLS MSLNKDSAKVGALLHGOWTLLOALOEMRDAAVRMAAEAOVSYLPVGIEHHFT.ELDHILGL LQEELRGPAKAAAKAPRPPGOPPRASSCLOPGIFLFYLLIOTVGFFGYVHFROELNKSLO

Important features of the protein: Signal peptide:

ECLSTGSLPLGPAPHTPRALGILRROPLPASMPA

WCG268268 (IB#7/E-AVO6206286 opc.)

Amino acids 1-23

Transmembrane domain:

Amino acids 215-232;450-465

N-glycosylation sites:

Amino acids 75-79;476-480

Glycosaminoglycan attachment site:

Amino acids

N-myristovlation sites:

Amino acids 78-84;122-128;126-132;168-174;172-178;

205-211;226-232;230-236;236-242;356-362

Amidation site:

Amino acids 102-106

Page 121 of 359

8/246

WC6268368 [Her//E/W/06266286 opc]

FIGURE 7

GCCCCAGCATGGCTGGCAGGGCTGGCCGCGGCGTGGCAGTGGCTCGCCGGCTGCTGGCT TCCGCGGTCTGCTCATGGCGCACAGCCAGCGGCTGCTCTTCCGAATCGGGTACAGCCTGTAC ACCCGCACCTGGCTCGGGTACCTCTTCTACCGACAGCAGCTGCGCAGGGCTCGGAATCGCTAC CCTAAAGGCCACTCGAAAACCCAGCCCCGCCTCTTCAATGGAGTGAAGGTGCTTCCCATCCC GCCATTCTGTGTACTCACAAGCACTGGGACCACAGTGGAGGGAACCGTGACCTCAGCCGGCG GCACCGGGACTGTCGGGTGTACGGGAGCCCTCAGGACGGCATCCCCTACCTCACCCATCCCC TGTGTCATCAAGATGTGGTCAGCGTGGGACGGCTTCAGATCCGGGCCCTGGCTACACCTGGC CACACAAGGCCATCTGGTCTACCTACTGGATGGGGAGCCCTACAAGGGTCCCTCCTGCCT CTTCTCAGGGGACCTGCTCTTCCTCTCTGGCTGTGGGCGGACCTTTGAGGGCAATGCAGAGA CCATGCTGAGCTCACTGGACACTGTGCTGGGGCTAGGGGATGACACCCTTCTGTGGCCTGGT CATGAGTATGCAGAGGAGAACCTGGGCTTTGCAGGTGTGGTGGAGCCCGAGAACCTGGCCCG GGAGAGGAGATGCAGTGGGTGCAGCGGCAGCGGCTGGAGCGCAAGGGCACGTGCCCATCTA CCCTGGGAGAGGGCGCTCCTACAACCCGTTCCTGAGAACCCACTGCCTGGCGCTACAGGAG GCTCTGGGGCCGGGCCCGACTGGGGATGATGACTACTCCCGGGCCCAGCTCCTGGA AGAGCTCCGCCGGCTGAAGGATATGCACAAGAGCAAGTGATGCCCCCAGCCCCCAGCCCA GCCCACTCCCCGCATGGGGAGGCCGCCACCACCACCCTCATCCTTCTCATCGCTAAC ACCACCACCTCCATCGGCACCCAAGCGGGCATCATCCCCCCACACTGCTCAGGGGAGGGGAG GGATCAGGCGATGAGACTGTGAGGCCAAAAGAAGGGGGCCTGTTGGAGGCTGGGAACCCCGC AGCGCGAGGCTGCCTCATCAACGGCAAGAGGAAAGGAGGGTCTCGGGACATCTCCAGACCC TACCAACTGGGAGGGTCCCCTCCTCCTTCCCTACTCCTGGGACGCAGCAAGGACATGGGGG CTGCTGTTAGCTTCTCCGTCAGGAGGCCTCATCTCACTGTAGCCCTGGAACCCAGGGTCCAT CTTGCCCTTCCCCCATCCATGGTTGGGAAAGAAGCTCAGCCCCTCACAGTGGCCTCAAGTGT GATGCCTTACAAAAGCACCACTCAGATGGGCAGCTGGACTCTGGTGTCCTGAGACTCTGCCC CTAAGAACACTGAAGGGCTGGAATGCTGGCTGGCCACTCTCTGCCTCAGTGGCCTCCCTACA GCCTGGAAGAAGGAGGGTCCTGATTGCCAAGGAAACCTCCTCATTGGGCTAAGGAGACACTG GAGTCTGGAGTGTGGAGCCCCACAGTCTTGCAGGTCACATGCTCTCCTTGCACATCTGGCCT GGTTGTACCCACTGGCCTCTGCCTCTGCCCAGGGCCAAAAGGGCCCCTCCTTGCCAGGGGAG AGACAGCCACGGTCCTCTTTGGCCGATGCTGTATTCTCATTTTGGCCCCTTGTTCTTAGGCCC GTCTGCCCGCCCTCCTCCATCTAACCTTTCCTGTTTTATCCGCAGCCCTTTTCTTCTTTGAG CCATGTGATTTCCCACTGGATCCAGGCCCCCATCCGGCTGGCAGGAGGGGGCTCTGACGTAC AGGTTGGAAATCAGAAGTCTGTGAGAGCGCGGGAGTGCATGGCAGCTCTGGGTCCCAGACCT GGCCCGACCCCTCTGCTTCACCTCCAGCTCTGCTGCTCCTCTACTCTTGGGTCGAGATCCCT TTGGAGCCACAGCGAGGAACCCTGTGGTCCTCAGGCAGGTGTACCTTGAGTCAGCCAGGAGC CCTCTTTTCCTGTGTCAAAGCCTGCCCTCGGGCTCTGCTCACCTCTGGTGACCCTCCAAGAT GCCCCTGCCCTCAGTTTCCCCTCATGATCTGGCCTCTGCCCCCTTCTCTAGCCACAGCCTCT GTTTCATGCCTCTGTGCCTTCGCTCATGCTGTTTCTTCCGACTGGAATGCCTTCCCCTGCTC CTCCTGCCTTGTCTGCCTGGCAAGTTCATCTCTCACGATCCCCTCAAAGGCCCCCTCCTCCA GGAAGGCAACCCCTGTGCCCCTCCCGGGCTACCTCTGCACTTTGTCAATGCTTCTCTT GTGGCACTTATCACACTGTATTTTACTTGTTTACATGTTTGTCTCCCCCTTCTAGACTGTGAA TCCTTAAGGGCATGGACTGTATCTTATGCATCTCTGTATTTCTGCGCCTAGCACGGTGCCTA

Page 122 of 359

9/246

FIGURE 8

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA96894 ><subunit 1 of 1, 361 aa, 1 stop

><MW: 40747, pI: 9.20, NX(S/T): 1

MAWQGWPAAWQWVAGCWLLLVLVLVLVSPRGCRARRGLRGLLMAHSQRLLFRIGYSLYT RTWLGYLFYRQQLRRARNRYPKGHSKTQPRLFNGVKVLPIPVLSDNYSYLIIDTQAQLAV AVDPSDPRAVQASIEKEGVTLVAILCTHKHWDHSGGNRDLSRRHRDCRVYGSPQDGIPYL THPLCHQDVVSVGRLQIRALATPGHTQGHLVYLLDGEPYKGPSCLFSGDLLFLSGCGRTF EGNAETMLSSLDTVLGLGDDTLLWPGHEYAEENLGFAGVVEPENLARERKMOWVORORLE RKGTCPSTLGEERSYNPFLRTHCLALOEALGPGPGPTGDDDYSRAOLLEELRRLKDMHKS K

Important features of the protein: 1 - 35

Signal peptide: Amino acids

WCG268268 (IB#7/E-AVO6206286 opc.)

N-glycosylation site:

Amino acids 106-110

Glycosaminoglycan attachment site:

Amino acids 234-238

cAMP- and cGMP-dependent protein kinase phosphorylation site: Amino acids 301-305

Tyrosine kinase phosphorylation site:

Amino acids 162-171

N-myristovlation sites:

Amino acids 41-47;235-241;242-248;303-309

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 6-17

cAMP phosphodiesterases class-II proteins:

Amino acids 144-161

10/246

FIGURE 9

WC0208088 [He ///E_AV-00208288 cpc.] Finge | 24 of 256

WO 02/08288 PCT/US01/21066

11/246

FIGURE 10

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA100272
><subunit 1 of 1, 108 aa, 1 stop
><MW: 12055, pI: 4.69, NX(s/T): 0
MMDHVESDQMAVIVLFSQLMYCFLLELAWYSEMYLCLRNCRYTGFGIERELVCRREVLEP
CLVPSLPADPVEYGPLPRGTGLSPARLPPTFLWICTRLLPSGGDGDLTV

Important features of the protein: Signal peptide:
Amino acids 1-30

N-myristoylation site: Amino acids 80-86

Page 125 of 359

12/246

WC0268268 [like]//E_W/06206286 opc.]

FIGURE 11

GGATTGAACAATCTGTAAACTAAAGGATCCTAATCATGAAAAATAAGTATGATAAATTATAAG TCACTATTGGCACTGTTGTTTATATTAGCCTCCTGGATCATTTTTACAGTTTTCCAGAACTC AGTCCTTATTCCCTAAAACACCACTGATATCATTAAAGCCACTAACAGAGACTGAACTCAGA CACCACCACCAGCGCCACATAGCACACCATCCTCAACCCTCGAGATACGTACTGCA GGGGAGACCAGCTGCACATCCTGCTGGAGGTGAGGGACCACTTGGGACGCAGGAAGCAATAT GGCGGGGATTTCCTGAGGGCCAGGATGTCTTCCCCAGCGCTGATGGCAGGTGCTTCAGGAAA GGTGACTGACTTCAACAACGGCACCTACCTGGTCAGCTTCACTCTGTTCTGGGAGGGCCAGG TCTCTCTGTCTCTGCTGCTCATCCACCCCAGTGAAGGGGTGTCAGCTCTCTGGAGTGCAAGG AACCAAGGCTATGACAGGGTGATCTTCACTGGCCAGTTTGTCAATGGCACTTCCCAAGTCCA CTCTGAATGTGGCCTGATCCTAAACACAAATGCTGAATTGTGCCAGTACCTGGACAACAGAG TATTCTAAGAACAAGAAGTTTCTTATCTTAGCAAACAAGAAAAGAGCCTCTTTGAAAGGTC AAATGTGGGTGTAGAGATTATGGAAAAATTCAATACAATTAGTGTCTCCAAATGCAACAAAG AAACAGTTGCAATGAAAGAGAAATGCAAGTTTGGAATGACATCCACAATCCCCAGTGGGCAT GTCTGGAGAAACACATGGAATCCTGTCTCCTGTAGTTTGGCTACAGTCAAAATGAAGGAATGC CAAAGCCAGTATCAACACACTGAAGTCAGTGGATCTGCATGAATCTGGAAAATTGCAACACC AGCTTGCTGTGGATTTGGATAGGAACATCAACATCCAGTGGCAAAAATATTGTTATCCCTTG ATAGGATCAATGACCTATTCAGTCAAAGAGATGGAGTACCTCACCCGGGCCATTGACAGAAC TGGAGGAGAAAAAATACTGTCATTGTTATTTCCCTGGGCCAGCATTTCAGACCCTTTCCCA TTGATGTTTTTATCCGAAGGGCCCTCAATGTCCACAAAGCCATTCAGCATCTTCTTCTGAGA AGCCCAGACACTATGGTTATCATCAAAACAGAAAACATCAGGGAGATGTACAATGATGCAGA AAGATTTAGTGACTTTCATGGTTACATTCAATATCTCATCATAAAGGACATTTTCCAGGATC TCAGTGTGAGTATCATTGATGCCTGGGATATAACAATTGCATATGGCACAAATAATGTACAC CCACCTCAACATGTAGTCGGAAATCAGATTAATATTATTAAACTATATTTGTTAAATAACAA

Page 135 of 359

WO 02/08288 PCT/US01/21066

13/246

FIGURE 12

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA108696

><subunit 1 of 1, 544 aa, 1 stop

><MW: 62263, pI: 9.17, NX(S/T): 7

MKISMINYKSLIALLFILASWIITTYPONSTKYWSALNLSISLHYWNNSTKSLFPKTPLI
SLKPLTETELRIKEIIEKLDQLIPPRFFTHVNTTTSATHSTATILNPRDTYCRGDQHHLL
LEVRDHLGRRKQYGGDTLRARMSSPALMAGASGKVTDFNNGTTLVSFTLFWEGQYSLSLL
LIHPSEGVSALWSARNOGYDRVIFTGQFVNGTSQVHSECGLILNTNAELCQYLDNRDQSG
FYCVRPGNHPCAALTHHYSKNKKVSVLSKQEKSLFERSNUVOEIMEKFNTISVSKCKNET
VAMKEKCKFGMTSTIPSGHVWRNTWNPVSCSLATVKMECLRGKLIYLMGDSTIROMMSY
FKASINTLKSVDLHESGKLQHQLAVDLDRNINIQWGKYCYPLIGSMTYSVKEMEYLTRAY
DRTGGEKNTVIVISLGGHFRPFIDVFIRRALNVHKAIQHLLLRSPDTMVIIKTENIREM
YNDABRFSDFHGYIQYLIIKDIPQDLSVSIIDAWDITIAYGTNNVHPPQHVVGNQINILL
NYIC

Important features of the protein:

Signal peptide:

WO0268268 [He://E-/W/00206286 opc]

Amino acids 1-22

N-glycosylation sites:

Amino acids 29-33;38-42;47-51;48-52;92-96;160-164;210-214

CAMP- and cGMP-dependent protein kinase phosphorylation site: Amino acids 262-266

Tyrosine kinase phosphorylation site:

Amino acids 236-243;486-494

N-myristovlation sites:

Amino acids 206-212;220-226;310-316;424-430;533-539

Amidation site:

Amino acids 127-131

Cell attachment sequence:

Amino acids 113-116

Page 127 of 359

14/246

WC0268268 [Be://E_W/06206286 opc]

FIGURE 13

TGGCATCCATTCCCCAAGTTCAGCCTAGGGACTCCACGTACCCCAGCTGGGTCTCATTGTTC CAGAACTGCATTAGTTAAGATTACCCAGACTTGGATTTCAAAGGAATACTTTCATTGTTCCG TCTGTAACACGAAGTAATTGGGGCCAGCTGGATGTCAGGATGCGTGTGGTTACCATTGTAAT GAGTGAATCATGGCCGGGCGGGTGGAGGCCGGAGAGGCTCCAACCCGGTCAAACGCTACGCA CCAGGCCTCCCGTGTGACGTGTACACATATCTCCATGAGAAATACTTAGATTGTCAAGAAAG AAAATTAGTTTATGTGCTGCCTGGTTGGCCTCAGGATTTGCTGCACATGCTGCTAGCAAGAA ACAAGATCCGCACATTGAAGAACAACATGTTTTCCAAGTTTAAAAAGCTGAAAAGCCTGGAT CACCCTCTTACTGCAGCACAACCAGATCAAAGTCTTGACGGAGGAAGTGTTCATTTACACAC CTCTCTGAGCTACCTGCGTCTTTATGACAACCCCTGGCACTGTACTTGTGAGATAGAAACG CTTATTCAATGTTGCAGATTCCCAGGAACCGGAATTTGGGGAACTACGCCAAGTGTGAAAG TCCACAAGAACAAAAAAAAAAAACTGCGGCAGATAAAATCTGAACAGTTGTGTAATGAAG AAAAGGAACAATTGGACCCGAAACCCCAAGTGTCAGGGAGACCCCCAGTCATCAAGCCTGAG GTGGACTCAACTTTTTGCCACAATTATGTGTTTCCCATACAAACACTGGACTGCAAAAGGAA AGAGTTGAAAAAAGTGCCAAACAACATCCCTCCAGATATTGTTAAACTTGACTTGTCATACA ATAAAATCAACCAACTTCGACCCAAGGAATTTGAAGATGTTCATGAGCTGAAGAAATTAAAC CTCAGCAGCAATGGCATTGAATTCATCGATCCTGCCGCTTTTTTAGGGCTCACACATTTAGA AGAATTAGATTTATCAAACAACAGTCTGCAAAACTTTGACTATGGCGTATTAGAAGACTTGT ATTTTTTGAAACTCTTGTGGCTCAGAGATAACCCTTGGAGATGTGACTACAACATTCACTAC CTCTACTACTGGTTAAAGCACCACTACAATGTCCATTTTAATGGCCTGGAATGCAAAACGCCT GAAGAATACAAAGGATGGTCTGTGGGAAAATATATTAGAAGTTACTATGAAGAATGCCCCAA AGACAAGTTACCAGCATATCCTGAGTCATTTGACCAAGACACAGAAGATGATGAATGGGAAA AAAAACATAGAGATCACACCGCAAAGAAGCAAAGCGTAATAATTACTATAGTAGGATAAGGT AGAAATTGTTCTGATTGTAATTAGTTTTGTATTTCTATACTGGTGTTAGAAAACATATGTT AATTATAAGTATTATTGTGACTATTATAGTAATCAAGAGAATGCTATCATCCTGCTTGCCTG TCCATTTGTGGAACAGCATCTGGTGATATGCAATTCCACACTGGTAACCTGCAGCAGTTGGG TCCTAATGATGGCATTAGACTTTCATAATGTCCTGTATAAATGTTTTTACTGCTTTTAGAAA ATAAAGAAAAAAACTTGGTTCATGTTTAAAA

Page 128 of 359

15/246

FIGURE 14

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA117935
><subunit 1 of 1, 440 aa, 1 stop</pre>

><MW: 51670, pI: 8.70, NX(S/T): 2

MRVVTIVILLCFCKAAELRKASPGSVRSRVNHGRAGGGRRGSNPVKRYAPGLPCDVYTYL
HEKYLDCCERKLVYVLPGWPODLLHHLLARNKIRTLKNNMFSKFKKLKSLDLQQNEISKI
ESSAFFGLNKLTTLLLGHNOLTKVLTESVEITYPLLSYLRLYDDWPHCTCEIETLISMLQI
PRNRNLGNYAKCESPOECKNKKLKQIKSEOLCNEEKECLDPKPOVSGRPPVIKPEVDSTF
CHNYVPPIOTLDCKRKELKKVPNNIPPDIVKLDLSYNKINOLRPKEFEDVHELKKLNLSS
NGIEFIDPAAFLGITHLEELDLSNNSLQNFDYGVLEDLYFLKLLWLRDDWRKCDYNIHYL
YYMLKHHYNVHFNGLECKTPEEYKGWSVGKYIRSYYEECPKDKLPAYPESFDQDTEDDEW
EKKHRDTHAKKOSVITIVG

Important features of the protein:

Signal peptide: Amino acids 1-15

WC0268268 [He://E-W/00206286 opc]

N-glycosylation sites: Amino acids 297-301;324-328

cAMP- and cGMP-dependent protein kinase phosphorylation sites: Amino acids 19-23;39-43;430-434

N-myristoylation sites: Amino acids 24-30;37-43

Amidation site:

Amino acids 37-41

Page 129 of 359

16/246

WC6008068 (Her//E/W/06206286 opc)

FIGURE 15

GCGCAGCAGCGCGGCCCCAGCAGCCTCGGCAGCCACCGCTGCAGCCGGGGCAGCCTC CGCTGCTGTCGCCTCTCTGATGCGCTTGCCCTCTCCCGGCCCCGGGACTCCGGGAGAATGT GGGTCCTAGGCATCGCGGCAACTTTTTGCGGATTGTTCTTGCTTCCAGGCTTTGCGCTGCAA ATCCAGTGCTACCAGTGTGAAGAATTCCAGCTGAACAACGACTGCTCCTCCCCCGAGTTCAT GGATCATGTACCGCAAGTCCTGTGCATCATCAGCGGCCTGTCTCATCGCCTCTGCCGGGTAC CAGTCCTTCTGCTCCCCAGGGAAACTGAACTCAGTTTGCATCAGCTGCTGCAACACCCCTCT TTGTAACGGGCCAAGGCCCAAGAAAAGGGGAAGTTCTGCCTCGGCCCTCAGGCCAGGGCTCC GCACCACCATCCTGTTCCTCAAATTAGCCCTCTTCTCGGCACACTGCTGAAGCTGAAGGAGA TGCCACCCCTCCTGCATTGTTCTTCCAGCCCTCGCCCCCAACCCCCACCTCCCTGAGTGA GTTTCTTCTGGGTGTCCTTTTATTCTGGGTAGGGAGCGGGAGTCCGTGTTCTCTTTTGTTCC AGTATGTACTTGAAGGAAGGAGGTGGAGTGAAAGTTCACCCCCATGTCTGTGTAACCGGAGT CAAGGCCAGGCTGGCAGAGTCAGTCCTTAGAAGTCACTGAGGTGGGCATCTGCCTTTTGTAA AGCCTCCAGTGTCCATTCCATCCCTGATGGGGGCATAGTTTGAGACTGCAGAGTGAGAGTGA CGTTTTCTTAGGGCTGGAGGGCCAGTTCCCACTCAAGGCTCCCTCGCTTGACATTCAAACTT CATGCTCCTGAAAACCATTCTCTGCAGCAGAATTGGCTGGTTTCGCGCCTGAGTTGGGCTCT AGTGACTCGAGACTCAATGACTGGGACTTAGACTGGGGCTCGGCCTCGCTCTGAAAAGTGCT TAAGAAAATCTTCTCAGTTCTCCTTGCAGAGGACTGGCGCCGGGACGCGAAGAGCAACGGGC GCTGCACAAAGCGGGCGCTGTCGGTGGTGGAGTGCGCATGTACGCGCAGGCGCTTCTCGTGG TTGGCGTGCTGCAGCGACAGGCGCAGCACAGCACCTGCACGAACACCCGCCGAAACTGCTG CGAGGACACCGTGTACAGGAGCGGGTTGATGACCGAGCTGAGGTAGAAAAACGTCTCCGAGA AGGGGAGGAGGATCATGTACGCCCGGAAGTAGGACCTCGTCCAGTCGTGCTTGGGTTTGGCC GCAGCCATGATCCTCCGAATCTGGTTGGGCATCCAGCATACGGCCAATGTCACAACAATCAG CCCTGGGCAGACACGAGCAGGAGGGGAGACAGAGA

Page 130 of 359

17/246

FIGURE 16

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA119474 ><subunit 1 of 2, 141 aa, 1 stop ><Wx: 15240, pri: 8.47, NX(S/T): 1 MWVLGIAATFCGLFLLPGFALQIQCYQCBEFQLNNDCSSPEFIVNCTVNVQDMCQKEVME

MWVLGIAATTCGLFILPCFALQIQCYQCEEFQLNNDCSSPEFIVNCTVNVQDMCQKEVME QSAGINYRKSCASSAACLIASAGYQSFCSPGKLNSVCISCCNTPLCNGPRPKKRGSSASA LRPGLRTIIIFLKLALFSAHC

Important features of the protein: Signal peptide:

Amino acids 1-22

WC0208268 [He://E-M/00206286 opc]

N-glycosylation site:

Amino acids 45-49

cAMP- and cGMP-dependent protein kinase phosphorylation site: Amino acids 113-117

N-myristoylation sites:

Amino acids 5-11;115-121;124-130

Ly-6 / u-PAR domain proteins:

Amino acids 94-107

Page 131 of 559

18/246

WC6268368 [Her//E/W/06266286 opc]

FIGURE 17

CGCAAAGCCGCCTCGGGGCGCTCATGGCGGGACGCCTCCTGGGAAAGGCTTTAGCCGCGGT GTCTCTCTCTGGCCTTGGCCTCTGTGACTATCAGGTCCTCGCGCTGCCGCGCGCATCCAGG CGTTCAGAAACTCGTTTTCATCTTGGTTTCATCTTAATACCAACGTCATGTCTGGTTCT AATGGTTCCAAAGAAATTCTCACAATAAGGCTCGGACGTCTCCTTACCCAGGTTCAAAAGT TGAACGAAGCCAGGTTCCTAATGAGAAAGTGGGCTGGCTTGTTGAGTGGCAAGACTATAAGC CTGTGGAATACACTGCAGTCTCTTGTCTTGGCTGGACCCAGGTGGGCAGATCCTCAGATCAGT GAAAGTAATTTTTCTCCCAAGTTTAACGAAAAGGATGGGCATGTTGAGAGAAAGAGCAAGAA GCCGGGGGCTTTTGGGGCGATGGGGCCCAAATCACGCTGCAGATCCCATTATAACCAGATGG AAAAGGGATAGCAGTGGAAATAAAATCATGCATCCTGTTTCTGGGAAGCATATCTTACAATT TGTTGCAATAAAAGGAAAGACTGTGGAGAATGGGCAATCCCAGGGGGGATGGTGGATCCAGGA GAGAAGATTAGTGCCACACTGAAAAGAGAATTTGGTGAGGAAGCTCTCAACTCCTTACAGAA AACCAGTGCTGAGAAGAGAGAAATAGAGGAAAAGTTGCACAAACTCTTCAGCCAAGACCACC GAAGCTGTGAACTACCATGACGAAACAGGTGAGATAATGGATAATCTTATGCTAGAAGCTGG AGATGATGCTGGAAAAGTGAAATGGGTGGACATCAATGATAAACTGAAGCTTTATGCCAGTC ACTCTCAATTCATCAAACTTGTGGCTGAGAAACGAGATGCACACTGGAGCGAGGACTCTGAA GCTGACTGCCATGCGTTGTAGCTGATGGTCTCCGTGTAAGCCAAAGGCCCACAGAGGAGCAT ATACTGAAAAGAAGGCAGTATCACAGAATTTATACTATAAAAAGGGCAGGGTAGGCCACTTG GCCTATTTACTTTCAAAACAATTTGCATTTAGAGTGTTTCGCATCAGAATAACATGAGTAAG ATGAACTGGAACACAAAATTTTCAGCTCTTTGGTCAAAAGGAATATAAGTAATCATATTTTG TATGTATTCGATTTAAGCATGGCTTAAATTAAATTTAAACAACTAATGCTCTTTGAAGAATC ATAATCAGAATAAAGATAAATTCTTGATCAGCTATA

Page 132 of 359

19/246

FIGURE 18

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA119498

><subunit 1 of 1, 350 aa, 1 stop

><MW: 39125, pI: 8.53, NX(S/T): 2

MAGRLIGKALAAVSILSLALASYTIRSSRCRGIQAFRNSFSSSWFHLNTNVMSGSNGSKEN SHNKARTSPYPGSKVERSQVPNEKVGWLVEWQDYKPVEYTAVSVLAGPRWADPQISESNF SPKFPEKDGHVERKSKWGLVEIENGRPRNPAGRTGLVGRGLIGRWGPNHAADPIITRWKR DSSGNKIMHPVSGKHILQFVAIKRKDCGEWAIPGGWVDPGEKISATLKREFGEEALNSLQ KTSAEKREIEEKLHKLFSQDHLVIYKGYVDDPRNTDNAWMETEAVNYHDETGEIMDNLML EAGDDAGKVKWVDINDKLKLYASHSOFIKLVAEKRDAHWSEDSBADCHAL

Important features of the protein:
Signal peptide:

Amino acids 1-20

WC0268268 [Her//E_W/06Z06286 opc.]

Amino acids 1-20

N-glycosylation site:
Amino acids 55-59

cAMP- and cGMP-dependent protein kinase phosphorylation site:

Amino acids 179-183

N-myristoylation sites: Amino acids 53-59:56-62

12.110 40243 30 33730

mutT domain signature: Amino acids 215-235

Page 133 of 359

WU 02/08288 PC 1/US01/2

WC0268268 [Be://E_WO0206286 opc]

20/246

FIGURE 19 GCCATGCAGCCATGTTCCGGGAGCCCTAATTGCACAGAAGCCCATGGGGAGCTCCAGACTGG CAGCCCTGCTCCTCCTCCTCATAGTCATCGACCTCTCTGACTCTGCTGGGATTGGC TTTCGCCACCTGCCCACTGGAACACCCGCTGTCCTCTGGCCTCCCACACGGATGACAGTTT CACTGGAAGTTCTGCCTATATCCCTTGCCGCACCTGGTGGGCCCTCTTCTCCACAAAGCCTT GGTGTGTGCGAGTCTGGCACTGTTCCCGCTGTTTGTGCCAGCATCTGCTGTCAGGTGGCTCA GGTCTTCAACGGGGCCTCTTCCACCTCCTGGTGCAGAAATCCAAAAAGTCTTCCACATTCAA GTTCTATAGGAGACACAAGATGCCAGCACCTGCTCAGAGGAAGCTGCTGCCTCGTCGTCACC TGTCTGAGAAGAGCCATCACATTTCCATCCCCTCCCCAGACATCTCCCACAAGGGACTTCGC TCTAAAAGGACCCAACCTTCGGATCCAGAGACATGGGAAAGTCTTCCCAGATTGGACTCACA AAGGCATGGAGGACCCGAGTTCTCCTTTGATTTGCTGCCTGAGGCCCGGGCTATTCGGGTGA CCATATCTTCAGGCCCTGAGGTCAGCGTGCGTCTTTGTCACCAGTGGGCACTGGAGTGTGAA GAGCTGAGCAGTCCCTATGATGTCCAGAAAATTGTGTCTGGGGGCCCACACTGTAGAGCTGCC TTATGAATTCCTTCTGCCCTGTCTGTGCATAGAGGCATCCTACCTGCAAGAGGACACTGTGA GGCGCAAAAAATGTCCCTTCCAGAGCTGGCCAGAAGCCTATGGCTCGGACTTCTGGAAGTCA GTGCACTTCACTGACTACAGCCAGCACACTCAGATGGTCATGGCCCTGACACTCCGCTGCCC ACTGAAGCTGGAAGCTGCCCTCTGCCAGAGGCACGACTGCCATACCCTTTGCAAAGACCTCC CGAATGCCACGGCTCGAGAGTCAGATGGGTGGTATGTTTTGGAGAAGGTGGACCTGCACCCC CAGCTCTGCTTCAAGTTCTCTTTTGGAAACAGCAGCCATGTTGAATGCCCCCACCAGACTGG GTCTCTCACATCCTGGAATGTAAGCATGGATACCCAAGCCCAGCAGCTGATTCTTCACTTCT CCTCAAGAATGCATGCCACCTTCAGTGCTGCCTGGAGCCTCCCAGGCTTGGGGCAGGACACT TTGGTGCCCCCGTGTACACTGTCAGCCAGGCCCGGGGCTCAAGCCCAGTGTCACTAGACCT CATCATTCCCTTCCTGAGGCCAGGGTGCTGTGTCCTGGTGTGGCGGTCAGATGTCCÁGTTTG CCTGGAAGCACCTCTTGTGTCCAGATGTCTCTTACAGACACCTGGGGCTCTTGATCCTGGCA CTGCTGGCCCTCCTCACCCTACTGGGTGTTGTTCTGGCCCTCACCTGCCGGCGCCCCACAGTC AGGCCCGGGCCCAGCGCGCCAGTGCTCCTCCTGCACGCGGCGGACTCGGAGGCGCAGCGGC GTGGACCTGTGGGAGGGAGGCACGTGGCGCGTGGGCCCGCTGCCGTGGCTCTGGGCGGC GCGGACGCGTAGCGCGGGAGCAGGGCACTGTGCTGCTGTGGAGCGGCGCCGACCTTC GCCCGGTCAGCGCCCCGACCCCCGCGCCGCCCCTGCTCGCCCTGCTCCACGCTGCCCCG CGCCCGCTGCTGCTCCCTTACTTCAGTCGCCTCTGCGCCAAGGGCGACATCCCCCCGCC GCTGCGCGCCTGCCGCGCTACCGCCTGCTGCGCGACCTGCCGCGTCTGCTGCGGGCGCTGG ACGCGCGCCTTTCGCAGAGGCCACCAGCTGGGGCCGCCTTGGGGCGCGGCAGCGCAGCCAG

AGCAGAGCTCCACCGCAGTCCCGGGTGTCT

Page 134 of 359

PCT/US01/21066

21/246

FIGURE 20

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA119502

><subunit 1 of 1, 667 aa, 1 stop
><MW: 74810, pI: 9.55, NX(S/T): 3</pre>

MGSSRLAALLIPLLLIVIDLSDSAGIGFRHLPHWNTRCPLASHTDDSFTGSSAYIPCRTW
MALFSTKPWCVRVMHCSSCLCOGLLSGGSGLORGI-PHLLVQKSKKSSTEKFYRRHKMPAP
AQRKLLPRRHLSEKSHHISIPSPDISHKGLRSKRTQPSDPETWESLPRLDSCRHGCPEFS
FDLLPEARAIRVTISSGPEVSVRLCHQWALECEELSSYYDVQKIVSGGHTVELPYEFFLLP
CLCIEASYLQEDTVRRKKCEPFGSWEBAYGSDFWKSVHFIDVSQHTQWVMALTIRCPLKLE
AALCORHDWHTLCKDLPNATARESDGWYVLEKVDLHPQLCFKFSFGMSSHVECPHGTGSL
TSMNVSMDTQAQOLLHFSSMHAITFSAMSLDELGGTLVPPYTYSQARGSPYSLDL
IIPFLRPGCCVLVWRSDVQFAWKHLLCPDVSYRHLGLLILALLTLLIGVVLALTCRRP
QSGPGARRVLLLHAADSEAQRRLVGALAELLRAALGGGRDVIVDLWEGRHVARVGPLPW
LWAARTRVARRGGYTLLHWSGADLRPVSGPPRARPLILLAHTRELLTLLFSVCAGGDIPPERRPLLLLAFSBLCAK
GDIPPERRALPRYRLLRDLPRLLRALDARPFAEATSWGRLGARQRRQSRLELCSRLEREA
ABLADLG

Important features of the protein: Signal peptide:

Amino acids 1-23

WCG268268 (IB#7/E-AVO6206286 opc.)

WO 02/08288

Transmembrane domain:

Amino acids 455-472

N-glycosylation sites:

Amino acids 318-322;347-351;364-368

Glycosaminoglycan attachment site:

Amino acids 482-486

cAMP- and cGMP-dependent protein kinase phosphorylation sites:

Amino acids 104-108;645-649

Tyrosine kinase phosphorylation site:

Amino acids 322-329

N-myristoylation sites:

Amino acids 90-96:358-364:470-476

Eukaryotic cobalamin-binding proteins:

Amino acids 453-462

Page 135 of 359

22/246

WC0268268 [like]//E_W/06206286 opc.]

FIGURE 21

CGGCTCGAGGCCCTTTGTGAGGGCTGTGAGCTGCGCCTGACGGTGGCACCATGAGCAGCTCA GGTGGGCGCCCGGGGCGTCCGCCAGCTCTGCGCCGCCGCGCAGGAAGAGGGCATGACGTG GTGGTACCGCTGTGTCGCCTGTCTGGGGTGCTGGGGGCAGTCTCTTGCGCGATCTCTG AATGCCTTCATCTTGTTGCTGTGAGGCGCCCTTCTGCTGCCAGTTCATCGAGTTTGCAAA CACAGTGGCGGAGAAGGTGGACCGGCTGCGCTCCTGGCAGAAGGCTGTCTTCTACTGCGGGA TGGCGGTCGTTCCCATCGTCATCAGCCTGACCCTGACCACGCTGCTGGGCAACGCCATCGCC TTTGCTACGGGGGTGCTGTACGGACTCTCTGCTCTGGGCAAAAAGGGCGATGCGATCTCCTA TGCCAGGATCCAGCAGCAGGCAGCAGGCGGATGAGGAGAAGCTCGCGGAGACCCTGGAGG GGGAGCTGTGAAGGGCTGGGCGCCCCTCCCTCCCTGTCCCCTCTTCTGGCTCTGTGTGGGTC CAAGTGAGGCCTGGACTGTCCACGCTGAGGCACAGCCTGGAGAGGGGCCTTTGCACGTGTCC CTACACCTGGAGTCCTCTGCTCCTTTCTCCAGACTGGCTTAAGCCAGGAGCCACTGGCTGCT GGTGTGAGGGTCTGGGCTGCTGGACTTGAGGCAGAGCCTGCAGCAGCTGTGTGGACACTACC CCTGCTGTGACCTGGGAGCAGCTTCCCCTGGAGATGCTGGTCCTGGCTTGAGGGGAGGGGCA AGTGGGACCCTGCCACCTGGGCACTGAGCAGAGGGACCTCCCCCAGCTCTCTTAGCAGGTGG AGCCCCAGGGCCTGGGACAGCCTGCCGCTGCCAGCAACCTCCCACTGCTGCCTAGGGTGCAG CGCCCACTGTCACCCTGCCTTCTGAAGAAGCCCACAGGGCTCCTAAGGTGCACCCCGGTACC GAACCTTGGACAGGCCACCTCAAGGCCCCTCGGCTGCCCCTCCTCCTGGGCCTGCTGGGGC CCCTAGGTTCTACCCATCACCCCCCCCCCCCCTGCTGCCCTTGGTGCTAAGGAAGTGGGGAAGAG CAGGCTCTCCCTGGCACCGAGGGTGCCCACCCTCTCCCTGGTGTGGCCCCGTCAACATCAGC CACAGCCCAGCCCCATTAGTGGGTTAGTGGGTCTGACCTCAGCCCCACTCAGGTGCTCCTGC TGGCCTGCCCAAGCCCTGCCCTCAGGGAGCTTCTGCCTTTTAAGAACTGGGCAGAGGCCACAGT CACCTCCCCACACAGAGCTGTCCCCACTGCCCTGGGTGCCAGGCTGTCCGGAGCCAGGCCTA CCCAGGGAGGATGCAGAGAGCTGGTGCCCAGGATGTGCACCCCCATATTCCCTCTGCCCTGT GGCCTCAGCCGCTGGCCTCTCTGACCGTGAGGCTGGCTCTCAGCCATCGGGCAGGTGCCTG TCTGGGGCCAACCCCAGGCTGGGCCTGCGCTGAGCTTCTGGAGCGCAGGTACTGGGTCTTGC TAAGTGAACTGTTTCCCAGGAACACCTCTCGGGCCCATCTGCGTCTGAGGCTGGGAGTGGCA TCTGAGGCCGGGGTGGCATCTGAGGCCAGGGTGGCAGGCTGGTGGGCTGGGGGTT TTCTGGGCCCTGCCCAGTACTGCCCTGGGGACTTGGTGGGCTCCTGGGTCAGCAGCATCCCA CCCCTGGGAGTCTGGCCAGCTGAGCCCCAGGGTGGCAGGGGCATTATAGCCTGGTGGACATG TGCCTTCAGGGTTCCTCCGGGGCCACCTTCCTCAGGCCAGTGCTGGGTTCAAAGGGCTGTGT GTGTGTGTTTTGTGTGTGTATGTATGTGTGTGGGTGCACACATCTGTCCCATGTATGCA CAGGTAGTGGGACCCCGGGCCCCTTCTGCCTGCCTGCTTCTGCCTTTCCAGAGGG TGTACCCTGTGGGGAAATGGTGGGTGCATGGCTGGATGCAGAGGTGGAAGGCCCTGGGCCAC AGGCGAGAGTGGGCGTGTCACCTGTCCCAGGTTCCCAGCAGTCTGCAGCTGTGCAGTCCTG GGGTCCCTGACCCTGTCGCCCAGGGGGCGTGCTGTCCAGCAGGGGCCCTGCCTTGCAAGGAA TTGTTTGTTCCTCTGTGTTCTGTGCGTCTTAAGCAATAAAGCGTGGCCGTGGGAAAAAAA

Page 136 of 359

23/246

FIGURE 22

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA119516
><subunit 1 of 1, 172 aa, 1 stop
><mW: 18470, pI: 5.45, NX(s/T): 0
MSSSGGAPGASASSAPPAQEEGMTWWYRNLCRLSGVIGAVSCAISGLFNCITHPLNIAA
GVWMINNAFILLICEAPFCCQFIEFANTVAEKVDRLRSWQKAVFYCGMAVVPIVISLITLT
TLIGNAIAFATTGVIYGISAIGKKGDAISYARIOOOROOADEEKLAETLEGEL

Important features of the protein: Signal peptide: Amino acids 1-42

AMILIO ACIOS 1-42

WC0208268 [Re://E/W/00206286 opc]

Transmembrane domains:

Amino acids 64-77;109-128

Tyrosine kinase phosphorylation site:

Amino acids 142-150

N-myristoylation sites:

Amino acids 5-11;6-12;9-15;35-41;38-44;46-52;124-130;132-138

Amidation site:

Amino acids 140-144

Page 137 of 359

WC0268268 [Be://E_W/06206286 opc]

24/246

FIGURE 23

Page 138 of 359

25/246

FIGURE 24

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA119530 ><subunit 1 of 1, 113 aa, 1 stop ><MW: 12799, pi: 7.53, NX(S/T): 1 MVLCSISLFLIFFHILFLNVSNYFLEVGHQECHSSLQCRDSGAGISEKVAISLLKLCPLL PSHLRSSP FIOOSSRLPARGFRDHRFSNPERLSTDLOLFOKLCWELGCDLEVN

Important features of the protein: Signal peptide:

Amino acids 1-18

WCG208268 [Re://E/W/00206286 opc]

N-glycosylation site: Amino acids 19-23

Glycosaminoglycan attachment site:

Amino acids 41-45

N-myristoylation site:

Amino acids 42-48

Page 139 of 359

26/246

WC6268368 [Her//E/W/06266286 opc]

FIGURE 25

CGGGCTCCGCGCGCTCCCACTTCCCGGCTCCCTTCGCCTCCAGGATGCGCTGAGCCCTACAA CACCCCAGCGCCCGCCCCCCCCCCACGAGGTGTGAATGACAGAGGTGGTGCCATCCAGCG CGCTCAGCGAGGTCAGCCTGCGCCTCCTCTGCCACGATGACATAGACACTGTGAAGCACCTG TGTGGCGACTGGTTCCCCATCGAGTACCCAGACTCATGGTATCGTGATATCACATCCAACAA GAAGTTCTTTTCCCTTGCTGCAACCTACAGAGGTGCCATTGTGGGAATGATAGTAGCTGAAA GACACAAGTCGCGTACATCCTAAGTCTGGGCGTCGTGAAAGAGTTCAGGAAGCACGGCAT AGGTTCCCTCTTACTTGAAAGTTTAAAGGATCACATATCAACCACCGCCCAGGACCACTGCA AAGCCATTTACCTGCATGTCCTCACCACCAACACACAGCAATAAACTTCTATGAAAACAGA GACTTCAAGCAGCACCACTATCTCCCCTATTACTACTCCATTCGAGGGGTCCTCAAAGATGG AGCACCTGGGCTCTGCACTAGCCAGCCTGAGCCCCTGCTCCATTCCGCACAGAGTCTACCGC CAGGCCCACAGCCTGCTGCAGCTTCCTGCCATGGTCGGGCATCTCTTCCAAGAGTGGCAT CGAGTACAGCCGGACCATGTGATGTCGGCTGGGCAGCCGCCACCAGGCCCCACCCTTCAGCC GCCCGCAGAGCCCGCCTTCCTGTCCATCTGACCCCTTCTGTTTTCTGCAAGGAGCTGCCAGC CATCTAACTGGGCTCGTCGGCCTGCCCCAGCTGCAGGCCCGGTGCTACACGGGCTCGGGAAC GCTTCTGGAAACCTCTGCCTGCCCTGGCCCTGCCCCCTGCGCATGCACCATCCCCAGG GCTGACCCAGTGTGGCTGCATTCACTGGGAGGGGCCTGCCCTCACTGGGCCTCTCCCACTCCG CTGCCTGTTCTTGCAGCTCCTTCCTGGAAAGCTGGAGGGACTTTCTCCTGCAAGGGAGAA CGCAAGTATTATGGACACACTTGACCGTAAAGGCACAGGAGCCTCGGAACAAGGGGGCGCAA TAAAGGGAATGGCCCGTCCCCTTCCAGAACCAGCCCAAAGAAGCCTGGGGGGTGAGGAGTGG CCCCCACTCCTCCATGAGGGGCTGATGAGGGGTGGGCAGCCTGGGGGAGGCTTTCCTCGCAA GCACAGAGCTCTGAGGCTCAGCCCCCTGGCACAGGCGGTCACGCATCAGGACGGTTCCTACT CCTCAGCACCTTCCGTGCAGTTACCAGTGCCCTGGGAGGTCACACTGCCCGTCGGACCTTGG CATGCTCCATTCAGCTGACCTGCTGAGGACAGGCATCGCCGAGACTCCTTGGGTCCTCCCCG CCCTCCTCATGCTGCCACAAGCTGCTGCTCCAAGGCCTGGCCACATGCAGACAGGAGGAAG CTGAGCTCGACATTAGGCCTCAAGGCTGCCATCTGTCTTGTAGGGCCTGGCCTTGTGGGCAG GGGGCAGTCCTGTGCCCTTGTGGGCCCTCAGCCTCTGAGGGCAGAGATGCTGTCAGTGCCGCA CCTGCCCTCCGATGCAGGGGTGGGGGGGGGGGGGTCCCGCCCAGCATAGCTGCAGTGTC ACAAAGCCATGGCAGAGGGTCCTAGCGGCGCCACCCTGCCCCAGCCTGAGGAGGAGGAGGAAG GGAGGAACAACCCTGGGCAGACGGGGTCTCAGGGACCTGTGTCCTTCCGCCTCCAGAGCTGC ${\tt CCAGCCACGGGCTCTCAGGGTGCTGGGGCCCCAGGTCCCCTCTTGAACTCAGCTGGGGCCCCCAGGTCCCCTCTTGAACTCAGCTGGGGCCCCAGGTCCCCAGGTCCCCTCTTGAACTCAGCTGGGGCCCCAGGTCCCCAGGTCCCCTCTTGAACTCAGCTGGGCCCCAGGTCCCCAGGTCCCCTCTTGAACTCAG$ CAGGGGCCCTCAGAATGAAGGCAGGCACCAGGCAGCAGCATCCCCCTCCTTGACGGTGC TGGCAGGAGGCCGCCCATGCTGACTGCTTGACCTCTGCTGACCTGACAGTGCTGGCGGG CAGCGCCTCTCCACTGCGAATCAGTGGCGATCATGTGATTTCTATTTCTGCCCCACAGGGT AAGGGACGAGTCTTCTGGAAGGCTCTGCCATGGACATTTGTCCTCGGGCTCAGAGGCCCCAC CCTGCCCCACACCTGCCCCTAATCACTGCAGTGTCCAGCCCAGTGTTGAACAGATTGTAGCG

Page 140 of 359

WO 02/08288 PCT/US01/21066

27/246

FIGURE 26

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA121772

><subunit 1 of 1, 242 aa, 1 stop

><MW: 27465, pI: 7.72, NX(S/T): 3

MTEVVPSSALSEVSLRLLCHDDIDTVKHLCGDWFPIEVPDSWYRDITSNKKFFSLAATYR GAIVGMIVAEIKNRTKIHKEDGDILATNFSVDTQVAYILSLGVVKEFRKHGIGSLLLESL KDHISTTAQDHCKAIYLHVLTTNNTAINFYENRDFKQHHVLPYYYSIRGVLKDGFTYVLY INGGHPWTILDYIQHLGSALASLSPCSIPHRVYRQAHSLLCSFLPWSGISSKSGIEYSR TM

N-glycosylation sites:

WC0208268 [Re://E/W/00206286 opc]

Amino acids 73-77;88-92;143-147

N-myristoylation sites:

Amino acids 61-67;65-71;198-204;235-241

Matrixins cysteine switch motif:

Amino acids 18-31

WO0268268 [He://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 141 of 359

28/246

FIGURE 27

GTTGGGCAGCACCCGCTCACCTCCATCCCCAGGACTTAGAGGGACGCAGGGCGTTGGG AACAGAGGACACTCCAGGCGCTGACCCTGGGAGGCCAGGACCAGGGCCAAAGTCCCGTGGGC AAGAGGAGTCCTCAGAGGTCCTTCATTCAGCGGTTCCGGGAGGTCTGGGAAGCCCACGGCCT GGCTGGGGCAGGGTCAACGCCGCCAGGCCGCCATGGTCCTGCTGCTGCTGCTTCTGGTG ATGGCTCTGCCCCAGGCACGACGGCGTCAAGGACTGCGTCTTCTGTGAGCTCACCGACTC CATGCAGTGTCCTGGTACCTACATGCACTGTGGCGATGACGAGGACTGCTTCACAGGCCACG CTTGAGGAACCCGTCAGCTACAGGGGCGTCACCTACAGCCTCACCAACTGCTGCACCGG CCGCCTGTGTAACAGAGCCCCGAGCAGCCAGACAGTGGGGGCCACCACCAGCCTGGCACTGG GGCTGGGTATGCTGCTTCCTCCACGTTTGCTGTGACCAACAGGGAGACAGGGCCTGGGACT GTTCTCCCAGATCCGCCACTCCCCATGTCCCCATGTCCTTCCCCCACTAAATGGCCAGAGAG GCCTGGACAACCTCTTGCGGCCCTGGCTTCATCCCTTCTAAGGCTGTCCACCAGGAGCCCG GTGCTAGGGGAAGCATCCCCAGGCCTGACTGAGCGGCAGGGGAGCACGGCCCGTGGGTTTGA TTGTATTACTCTGTTCCACTGGTTCTAAGACGCAGAGCTTCTCACATCTCAATCAGGATGCT

Page 142 of 359

29/246

FIGURE 28

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA125148 ><subunit 1 of 1, 124 aa, 1 stop ><MW: 13004, pi: 5.70, NX(S/T): 0 MW: CWILLLAWAL PROTUCKED TREMORESTYNHICEDER CETTCHCS

MVLCWLLLLVMALPPGTTGVKDCVFCELTDSMQCPGTYMHCGDDEDCFTGHGVAPGTGPV INKGCLRATSCGLEEPVSYRGVTYSLTTNCCTGRLCNRAPSSQTVGATTSLALGLGMLLP PRILL

Important features of the protein:

Signal peptide:

WCG268268 [Re://E/W/06266286 opc]

Amino acids 1-13

N-myristoylation sites:

Amino acids 19-25;52-58;64-70;81-87;106-112

Ly-6 / u-PAR domain proteins:

Amino acids 84-97

Page 143 of 359

WC0268268 [Be://E_W/06206286 opc]

30/246 FIGURE 29

GGCATTTTGAAAGCCCAGTGTTGCCCAGGGGGCATCTCCTTTGTGTTTATGAGAGACCTGCA TTCTCCCTGGCTCAGTTCTCTCAGGCTCTCCAGAGCTCAGGACCTCTGAGAAGAATGGAGCC CTCCTGGCTTCAGGAACTCATGGCTCACCCCTTCTTGCTGCTGATCCTCCTCTGCATGTCTC CTGTTTCCTGCACCCCTGCCCACTGGTTCTATGGCCACAAGGAGTTTTACCCAGTAAAGGA GTTTGAGGTGTATCATAAGCTGATGGAAAAATACCCATGTGCTGTTCCCTTTGTGGGTTGGAC CCTTTACGATGTTCTTCAGTGTCCATGACCCAGACTATGCCAAGATTCTCCTGAAAAGACAA GATCCCAAAAGTGCTGTTAGCCACAAAATCCTTGAATCCTGGGTTGGTCGAGGACTTGTGAC CCTGGATGGTTCTAAATGGAAAAAGCACCGCCAGATTGTGAAACCTGGCTTCAACATCAGCA TTCTGAAAATATTCATCACCATGATGTCTGAGAGTGTTCGGATGATGCTGAACAAATGGGAG GAACACATTGCCCAAAACTCACGTCTGGAGCTCTTTCAACATGTCTCCCTGATGACCCTGGA CAGCATCATGAAGTGTGCCTTCAGCCACCAGGGCAGCATCCAGTTGGACAGTACCCTGGACT CATACCTGAAAGCAGTGTTCAACCTTAGCAAAATCTCCAACCAGCGCATGAACAATTTTCTA CATCACAACGACCTGGTTTTCAAATTCAGCTCTCAAGGCCAAATCTTTTCTAAATTTAACCA AGAACTTCATCAGTTCACAGAGAAAGTAATCCAGGACCGGAAGGAGTCTCTTAAGGATAAGC TAAAACAAGATACTACTCAGAAAAGGCGCTGGGATTTTCTGGACATACTTTTGAGTGCCAAA AGCGAAAACACCAAAGATTTCTCTGAAGCAGATCTCCAGGCTGAAGTGAAAACGTTCATGTT TGCAGGACATGACACCACATCCAGTGCTATCTCCTGGATCCTTTACTGCTTGGCAAAGTACC CTGAGCATCAGCAGAGATGCCGAGATGAAATCAGGGAACTCCTAGGGGATGGGTCTTCTATT ACCTGGGAACACCTGAGCCAGATGCCTTACACCACGATGTGCATCAAGGAATGCCTCCGCCT CTACGCACCGGTAGTAAACATATCCCGGTTACTCGACAAACCCATCACCTTTCCAGATGGAC GCTCCTTACCTGCAGGAATAACTGTGTTTATCAATATTTGGGCTCTTCACCACAACCCCTAT TTCTGGGAAGACCCTCAGGTCTTTAACCCCTTGAGATTCTCCAGGGAAAATTCTGAAAAAAT ACATCCCTATGCCTTCATACCATTCTCAGCTGGATTAAGGAACTGCATTGGGCAGCATTTTG CCATAATTGAGTGTAAAGTGGCAGTGGCATTAACTCTGCTCCGCTTCAAGCTGGCTCCAGAC CACTCAAGGCCTCCCCAGCCTGTTCGTCAAGTTGTCCTCAAGTCCAAGAATGGAATCCATGT GTTTGCAAAAAAGTTTGCTAATTTTAAGTCCTTTCGTATAAGAATTAATGAGACAATTTTCCT ACCAAAGGAAGAACAAAAGGATAAATATAATACAAAATATATGTATATGGTTGTTTGACAAA TTATATAACTTAGGATACTTCTGACTGGTTTTGACATCCATTAACAGTAATTTTAATTTCTT TGCTGTATCTGGTGAAACCCACAAAAACACCTGAAAAAACTCAAGCTGACTTCCACTGCGAA GGGAAATTATTGGTTTGTGTAACTAGTGGTAGAGTGGCTTTCAAGCATAGTTTGATCAAAAC TCCACTCAGTATCTGCATTACTTTTATCTCTGCAAATATCTGCATGATAGCTTTATTCTCAG TTATCTTTCCCCATAATAAAAAATATCTGCCAAA

WC0268268 (Mer//E-/W/06Z06286 opc.) Page 144 of 359

> WO 02/08288 PCT/US01/21066

31/246

FIGURE 30

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA125150

><subunit 1 of 1, 505 aa, 1 stop

><MW: 59086, pI: 9.50, NX(S/T): 3

MEPSWLOELMAHPFLLLILLCMSLLLFOVIRLYORRRWMIRALHLFPAPPAHWFYGHKEF YPVKEFEVYHKLMEKYPCAVPLWVGPFTMFFSVHDPDYAKILLKRQDPKSAVSHKILESW VGRGLVTLDGSKWKKHROIVKPGFNISILKIFITMMSESVRMMLNKWEEHIAONSRLELF QHVSLMTLDSIMKCAFSHQGSIQLDSTLDSYLKAVFNLSKISNQRMNNFLHHNDLVFKFS SOGOIFSKFNOELHOFTEKVIODRKESLKDKLKODTTOKRRWDFLDILLSAKSENTKDFS EADLOAEVKTFMFAGHDTTSSAISWILYCLAKYPEHOORCRDEIRELLGDGSSITWEHLS OMPYTTMCIKECLRLYAPVVNISRLLDKPITFPDGRSLPAGITVFINIWALHHNPYFWED POVFNPLRFSRENSEKIHPYAFIPFSAGLRNCIGOHFAIIECKVAVALTLLRFKLAPDHS RPPOPVROVVLKSKNGIHVFAKKVC

Important features of the protein:

Signal peptide:

Amino acids

Transmembrane domain:

Amino acids 451-470

N-glycosylation sites:

Amino acids 145-149;217-221;381-385

cAMP- and cGMP-dependent protein kinase phosphorylation site:

Amino acids 264-268

N-myristoylation sites:

Amino acids 243-249;351-357;448-454;454-460

Cytochrome P450 cysteine heme-iron ligand signature:

Amino acids 445-455

Cytochrome P450 cysteine heme-iron ligand proteins: 442-473

Amino acids

FAD-dependent glycerol-3-phosphate dehydrogenase proteins:

Amino acids 124-141

Page 145 of 359

WO0268268 [He://E-/W/00206286 opc]

32/246

FIGURE 31

CCCACCTCTCCCGCCTGGCCTCCGCGGGAGTCCCCTACGATCCCGCTCAGCAGTGGGGCACT CGCTGAGGACAGCGAGTCCTGGGAGTGAGCCCAAGGCCACCCCTGGCCAGCCCAGGAGAGAT AGCCAGGCCAGCCCAGCCCGAGGCCAGGCTCTGGCCACGGCGGTCTCCGACATGGAGA GACATTGTCTGCTTTTATCCTGTTAACCTGTCTTCGGTGGTTGTGCCACGACATTCCCCAG GGTTCAGGTGCCCGGTGGCCGAGGGTCAGTCCAGTGGTAGAGCCTTGCTCTCCTAGGCTCAT CCTGCTGGCGGTCCTCCTGCTTCTGCTGTGTGTCACAGCTGGTTGTCCGGTTCTGCT GCCTCCGGAAGCAGGCACAGGCCAGCCACATCTGCCACCAGCACGCCAGCCCTGCGACGTG GCAGTCATCCCTATGGACAGTGACAGCCCTGTACACAGCACTGTGACCTCCTACAGCTCCGT GCAGTACCCACTGGGCATGCGGTTGCCCCTGCCCTTTGGGGAGCTGGACCTGGACTCCACGG CTCCTCCTGCCTACAGCCTGTACACCCCGGAGCCTCCACCCTCCTACGATGAAGCTGTCAAG ATGGCCAAGCCCAGAGAGGAAGGACCAGCACTCTCCCAGAAACCCAGCCCTCTCCTTGGGGC CTCGGGCCTAGAGACCACTCCAGTGCCCCAGGAGTCGGGCCCCAATACTCAACTACCACCTT GTAGCCCTGGTGCCCCTTGAAGGAGGTAGGAGAACGGACCAGAGCTTGGAGAACTAATGCTT GGAGCCAAGGGCCCAGCCCACCGTCCCACACATTGCTGTGGCCCCAACCTCGGTGC CATGTTACACCGGCCCCTGGCGTCACCCACTAGGCAGGCTGCTGCTTTCAGCCTCAGCCCCT GGCCCAGCCCAGCAGGCCCTCAGCCTGGAAGAGGCCCCTTGGGCCTAAGCCTCGGGTGGGA

33/246

Page 146 of 359

FIGURE 32

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA125151

><subunit 1 of 1, 194 aa, 1 stop

><MW: 20882, pI: 6.44, NX(S/T): 0

MERHCLLFILLTCLRWLCHDIPQGSGARWPRVSPVVEPCSPRLILLAVLLLLLCGVTAGC VRFCCLRKQAQAQPHLPPARQPCDVAVIPMDSDSPVHSTVTSYSSVQYPLGMKLPLPFGE LDLDSTAPPAYSLYTPEPPPSYDEAVKMAKPREEGPALSQKPSPLLGASGLETTPVPQES GPNTOLPPCSPGAP

Important features of the protein:

Signal peptide:

WC0208268 [Re://E/W/00206286 opc]

Amino acids 1-20

Transmembrane domain: Amino acids 39-58

N-myristoylation site:

Amino acids 55-61

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 50-61

Page 147 of 359

WC0268268 [Be://E_W/06206286 opc.]

34/246

FIGURE 33

CCTTGCTTGGTGCTTGGCACACACACACACTCGGTGGGCTACACAGGTTTTCCAGAAGCCCCAC GAGGTGGTAATGGTGCTGCTGATTCAGACCCTGGGGGCCCTCATGCCCTCGCTGCCCTCCTG CCTCAGCAACGGCGTGGAGAGGGCCAGGGCCCGAGCAGGAGCTCACCAGGCTGCTGGAGTTCT ACGACGCCACCCCCCCCCACTTCGCCAAGGGCTTGGAGATGGCACTGCTCCCCCCACCTACATGAA CACAATCTGGTAAAAGTCACGGAGCTGGTGGATGCTGTGTATGATCCATACAAACCCTACCAG CTGAAGTATGGCGACATGGAAGAGCAACCTCCTCATCCAGATGAGTGCTGTGCCTCTGGA GCATGGGGAAGTGATTGACTGTGTGCAGGAGCTGAGCCACTCCGTGAACAAGCTGTTTGGTC TGGCGTCTGCAGCCGTTGACAGATGCGTCAGATTCACCAATGGCCTGGGGACCTGCGGCCTG TTGTCAGCCCTGAAATCCCTCTTTGCCAAGTATGTGTCTGATTTCACCAGCACTCTCCAGTC CATACGAAAGAAGTGCAAACTGGACCACATTCCTCCCAACTCCCTCTTCCAGGAAGATTGGA CGGCTTTTCAGAACTCCATTAGGATAATAGCCACCTGTGGAGAGCTTTTGCGGCATTGTGGG CCAAGAACCCATGGCAAGAATATAATTACCTCCAGAAAGATAACCCTGCTGAATATGCCAGT ACCTCGAGCAGCGCTGACTCGGCTTAACCAGCAGGCCCACCAGCTGGCTTTCGATTCCGTGT TCCTGCGCATCAAACAACAGCTGTTGCTTATTTCGAAGATGGACAGCTGGAATACGGCTGGC ATCGGAGAAACCCTCACAGATGAACTGCCCGCCTTTAGTCTCACCCCTCTCGAGTACATCAG CAACATCGGGCAGTACATCATGTCCCTCCCCTGAATCTTGAGCCATTTGTGACTCAGGAGG ACTCTGCCTTAGAGTTGGCATTGCACGCTGGAAAGCTGCCATTTCCTCCTGAGCAGGGGGAT GCAGACCTACTGTGATGCGATCCTACAGATCCCTGAGCTGAGCCCACACTCTGCCAAGCAGC TGGCCACTGACATCGACTATCTGATCAACGTGATGGATGCCCTGGGCCTGCAGCCGTCCCGC ACCCTCCAGCACATCGTGACGCTACTGAAGACCAGGCCTGAGGACTATAGACAGGTCAGCAA AGGCCTGCCCGTCGCCTGGCCACCACCGTGGCCACCATGCGGAGTGTGAATTACTGACCCC ACCACACCGGACCACCAAGAGAGCCAGGGCTGCTGTTTCGTGACTCACCAGCACAGATTT GCTCAGAAACTCTGCCCAAGATTGGGCAGAAGTTACTTTAAAAAGACTTGGTTCAGCTGGTC ACGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCAAGCCAGATGGATCATGAGGCC AGGAGTTCGAGACCAGCCTGACCAACATGGTGAAAACCCCATCTCTACTAAAAATACAAAAAT TCAAAAAGAGTTGTAAATTAAAGATGTATTATTTATCAGAGAAGACTTTTTAGATAATTTTT TTAAAGGATCAGATCTTGAAAATGGAATAAATAACTACTGTGAAATGCAAAA

WCG268268 (IB#7/E-AV-06206236 opc.) Page 148 of 359

> WO 02/08288 PCT/US01/21066

35/246

FIGURE 34

```
></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA125181
```

><subunit 1 of 1, 491 aa, 1 stop

><MW: 54759, pI: 5.61, NX(S/T): 0

MVLLIOTLGALMPSLPSCLSNGVERAGPEOELTRLLEFYDATAHFAKGLEMALLPHLHEH NLVKVTELVDAVYDPYKPYOLKYGDMEESNLLIOMSAVPLEHGEVIDCVOELSHSVNKLF GLASAAVDRCVRFTNGLGTCGLLSALKSLFAKYVSDFTSTLOSIRKKCKLDHIPPNSLFO EDWTAFONSIRIIATCGELLRHCGDFEOOLANRILSTAGKYLSDSCSPRSLAGFOESILT DKKNSAKNPWOEYNYLOKDNPAEYASLMEILYTLKEKGSSNHNLLAAPRAALTRLNOOAH QLAFDSVFLRIKQQLLLISKMDSWNTAGIGETLTDELPAFSLTPLEYISNIGQYIMSLPL NLEPFVTQEDSALELALHAGKLPFPPEOGDELPELDNMADNWLGSIARATMOTYCDAILO IPELSPHSAKOLATDIDYLINVMDALGLOPSRTLOHIVTLLKTRPEDYROVSKGLPRRLA TTVATMRSVNY

Important features of the protein:

Signal peptide:

Amino acids 1-20

cAMP- and cGMP-dependent protein kinase phosphorylation site: Amino acids 242-246

N-myristoylation sites:

Amino acids 22-28;48-54;121-127;136-142;141-147;328-334; 447-453

Leucine zipper pattern:

Amino acids 295-317

Page 149 of 359

WC6268368 (Her//E/W/06266286 opc)

36/246

FIGURE 35

TGTCCCATCTCACTCCTGGGCCACCCATGGGGGCTGCTGGTAGCTGGTGTGTGGCTGCTGCTG GACTGTGTGGCAGTCCATCTGTCAGCAGCCACTGCGGGCCTACTTGCTGGGTGCCCAG CACCGCACTCACCACTGCAGGCGTGGCCAGGAGCGTGAGATCCCCAGAGCCCATGGCCAGTG AGAGGCGGCCAGGGATAGGTACCCAGGGAATGCCACAGGAGTTTGCTGGGCTCACGGAGCTC TTTCACTGGTCAGAGAGGGGTGTGTGTAGGAGAGGACTTCTACTTGGTGTTGAAGGACAGAT GCCAAGGCCCTCTGTGGGCAGGGGGGGGTGTTGAGGAGACTCGTCCAGCTGGGCAGA GGCTCATGTTGAGGGATGAGGCAGAGCTGGGGGGAGGAGGCCCAGAAATGGCAGGTCCTT GAATGCAGGTTTGGAAGCAGGGACGCCCTGTGAGGGTACAGAGTCTGGGCTGTTACCTTCTG TGGCTTTTGCTAGAAGGTGAGATGTCAGGGAGGAAGACAGGACTCCAGGATGTCTCCTGTCTCT CTCTGGAAAAAGGAGGTGGGCCCCTTTCTCAGCAGTCAGCTGCTGTTTTTTGAGGTCTTCTCC ATGGATAATCCACGGTGTTGGAAGTGGTTAAGGTAATGGATCCTCATGGGCTTACCATAAAA ATATCTGGAGGCTGGACCATTTTCCTTAAAACGTTATAAAAGCTGGAATTGAATGCCATCGG TGTCACCCCTGGGAAGTGTGCTTTCTCTTGAGCTCTTTTGGCCCCGAGATAGCAGTCACTCC ATAGTTTCGTGAAGACCAGCCTGGTGTTGCCTGGTTTTCTGCCATTAGGGAGCAGCTAGAGG TCTTCCAGTAGCTCCTGTGTAAAGTGATGAAAGAAAAGGGCTGGGTGCTGACTGCTCCTGGA GAAAAGCAACACTCCCAAAGTCTTAATTGCCTGCTTCCAGGGAGCTGTGGTGGTTTCCCT TGGGCAGGGCACACGCCCCAGTGGTTGACTTAATAAGGATACATTTTAATCAGAGGACAAAA ATGTGCCCTGACTTGATTTCCGCATGGGCTTCCAGCATGGTCAAAGG

Page 150 of 359

WO 02/08288 PCT/US01/21066

37/246

FIGURE 36

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA125192
><subunit 1 of 1, 139 aa, 1 stop</pre>

><MW: 14841, pI: 9.20, NX(S/T): 0

MGLLVAGVWLLLDCVAVHPSVSSHCGPTCWVPSTALTTAGVARSVRSPEPMASERRPGIG TQCMPQEFAGITELFHWSERSVCRRGLLLGVEGQMGFGWERGGMWAGLIGRREGESQGPL WAGRGGVURRLVOLGRGSC

Important features of the protein:

Signal peptide:

WC0208268 [He://E./W/00206286 opc]

Amino acids 1-22

N-myristoylation sites:

Amino acids 2-8;40-46;86-92;102-108;103-109

Amidation site:

Amino acids 109-113

WCG268268 [IB#7/E-AV-06206236 opc.]

WO 02/08288 PCT/US01/21066

Page 181 of 359

38/246

FIGURE 37

GGCCAGGAATGGGGTCCCCGGGCATGGTGCTGGGCCTCCTGGTGCAGATCTGGGCCCTGCAA GGCGACCCTGGTCTGCCAGGTGGACCAGGCCACAGCCTGGGAACGGCTCCGTGTTAAGTGGACA AAGGATGGGCCATCCTGTGTCAACCGTACATCACCAACGGCAGCCTCAGCCTGGGGGTCTG CGGGCCCAGGGACGCTCTCCTGGCAGCCACCCAGCCATCTCACCCTGCAGCTGGACCCTG TGAGCCTCAACCACAGCGGGGCGTACGTGTGCTGGGCGGCCGTAGAGATTCCTGAGTTGGAG GAGGCTGAGGGCAACATAACAAGGCTCTTTGTGGACCCAGATGACCCCACACAGAACAGAAA CCGGATCGCAAGCTTCCCAGGATTCCTCTTCGTGCTGCTGGGGGTGGGAAGCATGGGTGTGG CTGCGATCGTGTGGGGTGCCTGGTTCTGGGGCCGCCGCAGCTGCCAGCAAAGGGACTCAGGA AATGCATTCTACAGCAACGTCCTATACCGGCCCCGGGGGGCCCCAAAGAAGAAGAGTGAGGACTG CTCTGGAGAGGGGAAGGACCAGAGGGCCAGAGCATTTATTCAACCTCCTTCCCGCAACCGG CCCCCGCCAGCCGCACCTGGCGTCAAGACCCTGCCCCAGCCCGAGACCCTGCCCCAGCCCC GAGGCCAAAAGGGTTCCCCAAAGTGGGAGAGGAGTCAGAGATCCCAGGAGACCTCAACAGGA CCCCACCCATAGGTACACACAAAAAAGGGGGGATCGAGGCCAGACACGGTGGCTCACGCCTG TAATCCCAGCAGTTTGGGAAGCCGAGGCGGTGGAACACTTGAGGTCAGGGGTTTGAGACCA GCCTGGCTTGAACCTGGGAGGCGGAGGTTGCAGTGAGCCGAGATTGCGCCACTGCACTCCAG TGTCAGCCCCATCCTGAGACCCCGTCCTCATTTCTGTAATGATGGATCTCGCTCCCACTTTC

WC000808 Bits ## # W 05208288 opc] Fags 150 ot 350

WO 02/08288 PCT/US01/21066

39/246

FIGURE 38

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA125196

><subunit 1 of 1, 278 aa, 1 stop

><MW: 30319, pI: 9.21, NX(S/T): 3

MGSPGMVLGLLVQIWALQEASSLSVQQGPNLLQVRQGSQATLVCQVDQATAWERLRVKWT KDGAILCQPYITNGSLSLGVCEPQGRLSWQAFSHLTQLDPVSLNHSGAYVCHAAVEIPE LEEAEGNITRLFVDPDDPTQNRNRIASFPGFLFVLLGVGSMGVAAIVWGAWFWGRRSCQQ RDSGNAFYSNVLYRPRGAPKKSEDCSGEGKDQRGGSIYSTSFPQPAPRQPHLASRPCPSP RPCPSPRPGHPYSMVRVSPRPSFTQQPPRKGFPKVGF

Important features of the protein:

Signal peptide:

Amino acids 1-22

Transmembrane domain: Amino acids 149-166

N-qlycosylation sites:

Amino acids 73-77;105-109;127-131

Glycosaminoglycan attachment site: Amino acids 206-210

N-myristoylation sites:

Amino acids 5-11:37-43:63-69:108-114

Amidation site:

Amino acids 173-179

Page 183 of 359

WC6268368 [Her//E/W/06266286 opc]

WO 02/08288 PCT/US01/21066

40/246

FIGURE 39

ACCAGCAGAAGGCTGGGAGTCTGTAGTTTGTTCCTGCCGGGGCTCCACTGAGGGGAACGG GGACCTGTCTGAAGAGAAGATGCCCCTGCTGACACTCTACCTGCTCCTCTTCTGGCTCTCAG GCTACTCCATTGCCACTCAAATCACCGGTCCAACAACAGTGAATGGCTTGGAGCGGGGCTCC TTGACCGTGCAGTGTTTTACAGATCAGGCTGGGAGACCTACTTGAAGTGGTGGTGTCGAGG AGCTATTTGGCGTGACTGCAAGATCCTTGTTAAAACCAGTGGGTCAGAGCAGGAGGTGAAGA GGGACCGGGTGTCCATCAAGGACAATCAGAAAAACCGCACGTTCACTGTGACCATGGAGGAT CTCATGAAAACTGATGCTGACACTTACTGGTGTGGAATTGAGAAAACTGGAAATGACCTTGG GGTCACAGTTCAAGTGACCATTGACCCAGCACCAGTCACCCAAGAAGAAACTAGCAGCTCCC CAACTCTGACCGGCCACCACTTGGACAACAGGCACAAGCTCCTGAAGCTCAGTGTCCTCCTG CCCCTCATCTTCACCATATTGCTGCTGCTTTTTGGTGGCCGCCTCACTCTTGGCTTGGAGGATG ATGAAGTACCAGCAGAAAGCAGCCGGGATGTCCCCAGAGCAGGTACTGCAGCCCCTGGAGGG CGACCTCTGCTATGCAGACCTGACCCTGCAGCTGGCCGGAACCTCCCCGCGAAAGGCTACCA CGAAGCTTTCCTCTGCCCAGGTTGACCAGGTGGAAGTGGAATATGTCACCATGGCTTCCTTG CCGAAGGAGGACATTTCCTATGCATCTCTGACCTTGGGTGCTGAGGATCAGGAACCGACCTA CTGCAACATGGGCCACCTCAGTAGCCACCTCCCCGGCAGGGGCCCTGAGGAGCCCACGGAAT ACAGCACCATCAGCAGGCCTTAGCCTGCACTCCAGGCTCCTTCTTGGACCCCAGGCTGTGAG CACACTCCTGCCTCATCGACCGTCTGCCCCCTGCTCCCCTCATCAGGACCAACCCGGGGACT GGTGCCTCTGCCTGATCAGCCAGCATTGCCCCTAGCTCTGGGTTGGGCCTTGGGGCCAAGTCT CAGGGGCTTCTAGGAGTTGGGGTTTTCTAAACGTCCCCTCCTCTCCTACATAGTTGAGGAG GGGGCTAGGGATATGCTCTGGGGCTTTCATGGGAATGATGAAGATGATAATGAGAAAAATGT CATGTTATGGGCTGAATAATGGCCCCCAAAGATATCTGTGTCCTAATCCTCAGAACTTGTGA GAGAGGTTATTCTTGCTGATTCAGGTGGGCCCAAAATATCACCACAAGGGTCCTCATAAGAA AGAGGCCAGAAGGTCAAAGAGGTAGAGACAAAGTGATGGAGGTGGACGTGGGTGTGACG TGAGCAGGGCCATGAATGCCGCAGCCTTCAGATGCCAGAAAGGGAAAGGAATGGATTCCCC TGCCTGGAGCCTCCAAAAGAAACCAGCCCTGCCCACGCCTTGACTTGAGCCCATTGAAACTG ATCTTGAGCTCCTGGCCTCCAGAATTGCAGGAGAATAAATTTGTGTTGTTTTTAATGAAAAA

Page 154 of 359

41/246

FIGURE 40

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA125200

><subunit 1 of 1, 290 aa, 1 stop ><MW: 32335, pI: 5.82, NX(S/T): 1

MPLITLYLLIPWISGYSIATOITEPTTVAGLERGSLTVOCVYRSGWETYLKWWCRGAIWR OCKILVKTSGSEQEVKRDRVSIKDNQKNRTFTVTMEDLMKTDADTYWCGIEKTGNDLGVT VQVTIDPAPVTQEETSSSPTLTGHHLDNRHKLIKLSVLLPLIFTILLLLIVAASLLAWRM MKYQQKAAGMSPEQVLQPLEGDLCYADLTLQIAGTSPRKATTKLSSAQVDQVEVEYVTMA SIJKEDISYASITIGAS BODETYCNNGHLSSHLPGRGEEFTEYSTISRP

Important features of the protein: Signal peptide:

Amino acids 1-15

WC0268268 (Her//E-/WO0Z06286 opc.)

Transmembrane domain: Amino acids 155-174

N-glycosylation site: Amino acids 88-92

cAMP- and cGMP-dependent protein kinase phosphorylation site:
Amino acids 218-222

Tyrosine kinase phosphorylation site: Amino acids 276-285

AMILIO ACIUS 270-263

N-myristoylation sites: Amino acids 30-36;109-115;114-120

Page 185 of 359

42/246

WC0268268 [Be://E_W/06206286 opc.]

FIGURE 41

AAGAACACTGTTGCTCTTGGTGGACGGGCCCAGAGGAATTCAGAGTTAAACCTTGAGTGCCT GCGTCCGTGAGAATTCAGCATGGAATGTCTCTACTATTTCCTGGGATTTCTGCTCCTGGCTG CAAGATTGCCACTTGATGCCGCCAAACGATTTCATGATGTGCTGGGCAATGAAAGACCTTCT GCTTACATGAGGGAGCACAATCAATTAAATGGCTGGTCTTCTGATGAAAATGACTGGAATGA AAAACTCTACCCAGTGTGGAAGCGGGGAGACATGAGGTGGAAAAACTCCTGGAAGGGAGGCC GTGTGCAGGCGGTCCTGACCAGTGACTCACCAGCCCTCGTGGGCTCAAATATAACATTTGCG GTGAACCTGATATTCCCTAGATGCCAAAAGGAAGATGCCAATGGCAACATAGTCTATGAGAA GAACTGCAGAAATGAGGCTGGTTTATCTGCTGATCCGTATGTTTACAACTGGACAGCATGGT CAGAGGACAGTGACGGGGAAAATGGCACCGGCCAAAGCCATCATAACGTCTTCCCTGATGGG AAACCTTTTCCTCACCACCCCGGATGGAGAGATGGAATTTCATCTACGTCTTCCACACACTT GGTCAGTATTTCCAGAAATTGGGACGATGTTCAGTGAGAGTTTCTGTGAACACAGCCAATGT GACACTTGGGCCTCAACTCATGGAAGTGACTGTCTACAGAAGACATGGACGGGCATATGTTC CCATCGCACAAGTGAAAGATGTGTACGTGGTAACAGATCAGATTCCTGTGTTTGTGACTATG TTCCAGAAGAACGATCGAAATTCATCCGACGAAACCTTCCTCAAAGATCTCCCCATTATGTT TGATGTCCTGATTCATGATCCTAGCCACTTCCTCAATTATTCTACCATTAACTACAAGTGGA GCTTCGGGGATAATACTGGCCTGTTTGTTTCCACCAATCATACTGTGAATCACACGTATGTG CTCAATGGAACCTTCAGCCTTAACCTCACTGTGAAAGCTGCAGCACCAGGACCTTGTCCGCC ACCGCCACCACCACCAGACCTTCAAAACCCACCCCTTCTTTAGCAACTACTCTAAAATCTT ATGATTCAAACACCCCAGGACCTACTGGTGACAACCCCCTGGAGCTGAGTAGGATTCCTGAT GAAAACTGCCAGATTAACAGATATGGCCACTTTCAAGCCACCATCACAATTGTAGAGGGAAT CTTAGAGGTTAACATCATCCAGATGACAGACGTCCTGATGCCGGTGCCATGGCCTGAAAGCT CCCTAATAGACTTTGTCGTGACCTGCCAAGGGAGCATTCCCACGGAGGTCTGTACCATCATT TCTGACCCCACCTGCGAGATCACCCAGAACACAGTCTGCAGCCCTGTGGATGTGGATGAGAT GTGTCTGCTGACTGTGAGACCAACCTTCAATGGGTCTGGGACCTACTGTGTGAACCTCACCC TGGGGGATGACACAAGCCTGGCTCTCACGAGCACCCTGATTTCTGTTCCTGACAGAGACCCA GCCTCGCCTTTAAGGATGGCAAACAGTGCCCTGATCTCCGTTGGCTGCTTGGCCATATTTGT CACTGTGATCTCCCTCTTGGTGTACAAAAAACACAAGGAATACAACCCAATAGAAAATAGTC CTGGGAATGTGGTCAGAAGCAAAGGCCTGAGTGTCTTTCTCAACCGTGCAAAAGCCGTGTTC TTCCCGGGAAACCAGGAAAAGGATCCGCTACTCAAAAACCAAGAATTTAAAGGAGTTTCTTA ATTTCGACCTTGTTTCTGAAGCTCACTTTTCAGTGCCATTGATGTGAGATGTGCTGGAGTG GCTATTAACCTTTTTTTCCTAAAGATTATTGTTAAATAGATATTGTGGTTTTGGGGAAGTTGA AGCCATGTTGTGAAACTGATAAAAGCAACTTAGCAAGGCTTCTTTTCATTATTTTTTATGTT TCACTTATAAAGTCTTAGGTAACTAGTAGGATAGAAACACTGTGTCCCGAGAGTAAGGAGAG AAGCTACTATTGATTAGAGCCTAACCCAGGTTAACTGCAAGAAGAGGCGGGATACTTTCAGC TTTCCATGTAACTGTATGCATAAAGCCAATGTAGTCCAGTTTCTAAGATCATGTTCCAAGCTA ACTGAATCCCACTTCAATACACACTCATGAACTCCTGATGGAACAATAACAGGCCCAAGCCT TATTTTGGTGACAACCTACTTTGCTTGGCTGAGTGAAGGAATGATATTCATATATTCATTTA TTCCATGGACATTTAGTTAGTGCTTTTTATATACCAGGCATGATGCTGAGTGACACTCTTGT GTATATTTCCAAATTTTTGTACAGTCGCTGCACATATTTGAAATCATATATTAAGACTTTCC AAAGATGAGGTCCCTGGTTTTTCATGGCAACTTGATCAGTAAGGATTTCACCTCTGTTTGTA GTGTGGGAAGAGACA

Page 156 of 359

WO 02/08288 PCT/US01/21066

43/246

FIGURE 42

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA125214

><subunit 1 of 1, 572 aa, 1 stop

><MW: 63953, pI: 6.55, NX(S/T): 12

MECLYYFLGFLLLAARLPLDAAKRFHDVLGNERPSAYMREHNOLNGWSSDENDWNEKLYP VWKRGDMRWKNSWKGGRVOAVLTSDSPALVGSNITFAVNLIFPRCOKEDANGNIVYEKNC RNEAGLSADPYVYNWTAWSEDSDGENGTGOSHHNVFPDGKPFPHHPGWRRWNFIYVFHTL GOYFOKLGRCSVRVSVNTANVTLGPOLMEVTVYRRHGRAYVPIAOVKDVYVVTDOIPVFV TMFQKNDRNSSDETFLKDLPIMFDVLIHDPSHFLNYSTINYKWSFGDNTGLFVSTNHTVN HTYVLNGTFSI.NI.TVKAAAPGPCPPPPPPPPPPPPPSIATTI.KSYDSNTPGPTGDNPI.E LSRIPDENCOINRYGHFOATITIVEGILEVNIIOMTDVLMPVPWPESSLIDFVVTCOGSI PTEVCTIISDPTCEITQNTVCSPVDVDEMCLLTVRRTFNGSGTYCVNLTLGDDTSLALTS TLISVPDRDPASPLRMANSALISVGCLAIFVTVISLLVYKKHKEYNPIENSPGNVVRSKG LSVFLNRAKAVFFPGNOEKDPLLKNOEFKGVS

Important features of the protein: Signal peptide:

Amino acids

WO0268268 [Be://E-W/00206286 opc]

1-21

Transmembrane domain:

Amino acids 496-516

N-glycosylation sites:

Amino acids 93-97;134-138;146-150;200-204;249-253;275-279; 296-300;300-304;306-310;312-316;459-463;467-471

N-myristoylation sites:

91-97;147-153;290-296;418-424 Amino acids

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 496-507

Cell attachment sequence:

Amino acids 64-67

Page 187 of 359

44/246

WC6268368 [Her//E/W/06266286 opc]

FIGURE 43

CAGAGCTTGCACCTGCCAGTCCATCTGACATCAAAGCCAGTGTCTCTAATGGTGACACCACC CTCCTCTGCAGCAGGAGGCAGAGCTGTGGGATGAATGAGGTTCGCCAGGTCTCCCTTACCTA TCCTGGGTCCCCAGCTCCTTCTCACTCTCTCCCTTGCAGCCTCGAAGCGGAGGATCCCTGT GTCCCAGCCGGGCATGCCCGACCCCACCAGCTTTTCGATGACACAAGTTCAGCCCAGAGCC GGGGCTATGGGGCCCAGCGGGCACCTGGTGGCCTGAGTTATCCTGCAGCCTCTCCCACGCCC CATGCAGCCTTCCTGGCTGACCCGGTGTCCAACATGGCCATGGCCTATGGGAGCAGCCTGGC CGCGCAGGGCAAGGAGCTGGTGGATAAGAACATCGACCGCTTCATCCCCATCACCAAGCTCA AGTATTACTTTGCTGTGGACACCATGTATGTGGGCAGAAAGCTGGGCCTGCTGTTCTTCCCC TACCTACACCAGGACTGGGAAGTGCAGTACCAACAGGACACCCCGGTGGCCCCCCGCTTTGAC GTCAATGCCCGGACCTCTACATTCCAGCAATGGCTTTCATCACCTACGTTTTGGTGGCTGG TCTTGCGCTGGGGACCCAGGATAGGTTCTCCCCAGACCTCCTGGGGCTGCAAGCGAGCTCAG CCCTGGCCTGACCCTGGAGGTGCTGGCCATCCTGCTCAGCCTCTATCTGGTCACTGTC AACACCGACCTCACCATCGACCTGGTGGCCTTCTTGGGCTACAAATATGTCGGGATGAT TGGCGGGGTCCTCATGGGCCTGCTCTTCGGGAAGATTGGCTACTACCTGGTGCTGGGCTGGT GCTGCGTAGCCATCTTTGTGTTCATGATCCGGACGCTGCGGCTGAAGATCTTGGCAGACGCA GCAGCTGAGGGGGTCCCGGTGCGTGGGGCCCGGAACCAGCTGCGCATGTACCTGACCATGGC GGTGGCGGCGCGCAGCCTATGCTCATGTACTGGCTCACCTTCCACCTGGTGCGGTGAGCGC GCCCGCTGAACCTCCCGCTGCTGCTGCTGCTGGGGGGCCACTGTGGCCGCCGAACTCATC TCCTGCCTGCAGGCCCCAAGGTCCACCCTGTCTGGCCACAGGCACCGCCTCCATCCCATGTC CCGCCCAGCCCCCCAACCCAAGGTGCTGAGAGATCTCCAGCTGCACAGGCCACCGCCC AAAAAGA

Page 158 of 359

45/246

FIGURE 44

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA125219

><subunit 1 of 1, 283 aa, 1 stop

><MW: 31175, pI: 7.51, NX(S/T): 0

MADPHOLFDDTSSAQSRGYGAQRAPGGLSYPAASFTPHAAFLADPYSNMAMAYGSSLAAQ GKELUDKAI DRFIPITKLKYYFAVDTMYYGRKLGIL FPFYLHQDWEVYQYQOTP VAPRFD VNAPDLYIPAMAFITYVLVAGLALGTQDRFSPDLLGLQASSALAWLTLEVLAILLSLYLV TVNTDLTTIDLVAFLGYKYYGMIGGVLMGLLFGKIGYYLVLGWCCVAIFVFMIRTLRLKI LADAAABGYPYGGANOLGWYLTMAVAAQOMLMYWLTFHLVR

Important features of the protein:

Transmembrane domain:

Amino acids 126-142;164-179;215-233

N-myristoylation sites:

Amino acids 54-60;141-147;156-162;201-207;205-211;209-215

Amidation site:

WCG208268 [Re://E/W/00206286 opc]

Amino acids 89-93

WCG268268 [IBe://E-AVO6206236 opc.]

WO 02/08288 PCT/US01/21066

Page 189 of 359

46/246

FIGURE 45

GCTGAGCACCAACAGGAACTATTCCAGTGAAGAGCAAGTGCTGCCCGACCCAGGACCCTGTG TAGCTGGGATGTCTCACTCCAGTTGCTCAGGTTCACCCAGGAAGCTCCTCCGTGGAGTGGCC TTGAATGTGAAGACTGCTGAAGTCAGCTGGCTTCACTTGAGCTGCAGAAAAGGTGGCTGGGA TGGCCCAGGTGCACCCAGAGGCCCCAGCCCTTTGGCTGCCTTTGGGTTGTGACTTGGGTTGT TGCCTCATGGAACCAGGAGTCCCAAAAAGTCAGGAGCCTGGAGGCTCTGAAAGGAGCAGGGA TTCCATAGTGCGTGAAGCTGAAATAGGCGCCCTCCTGGGGAGCCCCCAGCAAAACTGTTTTT CATACCCACTCCCAGAACTGCCCCGCTCCAGCTCCAGCGCCAGCGCCAGCTGGTTGCCAGGC GTCATTGGAGAGGCCTGCCCCAGGGGCAGCAGGGAGTGGTGGACCTGTATGGGCTGGC AGGAGGCCATTGGCCATGCTGACAAGTGTCACCTGCCTTCCTAGCCTGGAGCCACCCCTCAG GTGGCCTGCTTGCACCTCCTATCCGGAGGTAGCCTGCCCCACCTGTAGGCAGAGGGGGCTCT TGCTTGAGGCCTGCACAGGAAGCAAGTATAGCCCCGGTGCCCCAGAGTGGGTTCCACTTAGC CCTGGCGAGATGGCCTGTCCTGAGATCTCTGCTCCCAGACCCCACCATCTGGGGAGCACAGT CCTTAGGCTGCCTGGTCCAGGAAGGGGGTGCGGCTCTGTCAGGAAACCTGGACTCTCAAGGC CCACCAGCCTCTCCGTGAGTGTTAGAAATCACAGATACAGTATATACTTAATTACACTACTC ACTACTCAAAAAAAAAAAAAAAAAA

Page 180 of 359

47/246

FIGURE 46

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA128309
><subunit 1 of 1, 97 aa, 1 stop
><dw: 10112, pI: 8.64, Nx(s/T): 0
MSHSSCSGSPRKLLRGVASIILALSSLAAHATPAWAFCSLMLDEPLPPQCFSKTDPPEAS
LNVKTAEVSWHIHLSCRKGGWGPCFASPEGSPLAAFGL

Important features of the protein:
Signal peptide:
Amino acids 1-31

WC0208268 [Re#//E/W/00206286 opc]

Page 181 of 359

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288 PCT/US01/21066

48/246

FIGURE 47

TTCCGGGCCCTGGCGTCTCGTCTCCTTACCCTGGGGCTACCCTTGCCCGGTCCTACTGCCCG CGGTTAACCCGCCGAGCCGCCTCTCCCCTCCCCGACTCAACCCTGCCCTCCCCCGT GCTTTGCAGACGCCGCCGGGGGCCCAGGCGGCTGATGCGTGTGGGCCTCGCGCTGATCTTG GTGGGCCACGTGAACCTGCTGCTGGGGGCCGTGCTGCATGGCACCGTCCTGCGGCACGTGGC CAATCCCCGCGGCGCTGTCACGCCGGAGTACACCGTAGCCAATGTCATCTCTGTCGGCTCGG GGCTGCTGAGCGTTTCCGTGGGACTTGTGGCCCTCCTGGCGTCCAGGAACCTTCTTCGCCCT CCACTGCACTGGGTCCTGGCACTAGCTCTGGTGAACCTGCTCTTGTCCGTTGCCTGCTC CCTGGGCCTCCTTCTTGCTGTCACTCACTGTGGCCAACGGTGGCCGCCGCCTTATTGCTG ACTGCCACCCAGGACTGCTGGATCCTCTGGTACCACTGGATGAGGGGCCGGGACATACTGAC TGCCCCTTTGACCCCACAAGAATCTATGATACAGCCTTGGCTCTCTGGATCCCTTCTTTGCT GAGTTGGGCCCTGCAGGAAGGACGGACTTCAGGGGCAGCTAGAGGAAATGACAGAGCTTGAA TCTCCTAAATGTAAAAGGCAGGAAAATGAGCAGCTACTGGATCAAAATCAAGAAATCCGGGC ATCACAGAGAAGTTGGGTTTAGGACAGGTGCTGTTCCGAGACTCAGTCCTAAAGGGTTTTTT TTCCCACTAAGCAAGGGGCCCTGACCTCGGGATGAGATAACAAATTGTAATAAAGTAACTTC

MCG008058 (like W.E. VA.Oxfoesse obc) Eadin 185 of 028

WO 02/08288 PCT/US01/21066

49/246

FIGURE 48

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA129535
><subunit 1 of 1, 222 aa, 1 stop</pre>

><MW: 23566, pI: 6.70, NX(S/T): 0

MRVGLALILVGHVNLLLGAVLHGTVLRHVANPRGAVTPEYTVANVISVGSGLLSVSVGLV ALLASRNLLRPPLHWVLLALALVNLLLSVACSIGLLLAVSLTVANGGRRLIADCHPGLLD PLVPLDGGPGHTDCPFDPTRIYDTALALWIPSLLMSAGEAALSGYCCVAALTLRGVGPCR KDOLQGQLEEMTELESFKCRQENEQLLDQNQEIRASGR

Important features of the protein: Signal peptide:

Amino acids 1-18

Transmembrane domain:

Amino acids 44-60;76-96

N-myristoylation sites:

Amino acids 94-100;175-181

Amidation site:

Amino acids 106-110

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 81-92

Page 183 of 359

WC0268268 [Be://E-W/00206286 opc]

50/246

FIGURE 49

WC0008088 (He ///E NVOV208288 opt.) Page (84 of 55)

WO 02/08288 PCT/US01/21066

51/246

FIGURE 50

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA129549
><subunit 1 of 1, 133 aa, 1 stop
><MM: 14792, pi: 5.97, NX(s/T): 0
MALGVPISVYLLFNAMTALTEEAAVTVTPPITAQQADNIEGPIALKFSHLCLEDHNSYCI
NGACAPHHELEKAICRCFTGYTGERCEHLTLTSYAVDSYEKYIAIGIGVGLLLSGFLVIF
YCVIRKRYEKDKI

Important features of the protein: Signal peptide:

1-20 (weak)

Transmembrane domain:

103-117

N-myristoylation site. 4-10;106-112;110-116

EGF-like domain cysteine pattern signature. 75-87

Integrins beta chain cysteine-rich domain proteins 66--88

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 185 of 359

52/246

FIGURE 51

GGCTCGAGCTTGGCTCTCAGACCATCCTGGTGGAAGAACACTAGCAGTCTGCCCAATCTGA **ATG**CAAATCCAGAATAATCTTTTCTTTTGTTGTTACACAGTTATGAGTGCAATTTTTAAATG GCTGCTACTCTACAGCCTGCCTTATGCTTTCTCCTGGGCACGCAGGAAAGTGAGAGCT TCCACTCCAAAGCAGAGATCCTAGTGACACTAAGTCAGGTAATAATCTCTCCAGCTGGACCT CATGCACTCACATGGACAACACACTTCTCTCTTCAGTGATCATCATCTTGTACCATGTTG GTGGCATGCTGTAATCGTGACTCAACATCCGGTTGCCAATTGCTATGTAACAAACCACCTCA ACATTCAGTGGCTTGAATTGAAAGCAGGGTCTTGAAGAGATATTTGCACATTTCATCCTCCC AGCAGCATTATTCACAACAGCCAATAGGCAGAAGCAACCCAATGTCCAACCATAGATGAGTG TCCCGCCACGTGCTACAACATGGATGGACCTTGAGGACACTATGCTAAGTGAAGTAAGCCAG GCACAAAAGGACAAATACTCTATGATTCCATTTTATAGGGTACCAAAGAGAATCAAACTCAC AGAGATAGAAAGTAGACTGGGGTGGCCAGGGACTCGGGGAGAGAGGGAAAGGGCAGTTATTGT TTAAAAGGTACAGAGTTTCAGTTTGGGAAGATGAAAATGTTCTGGAAACGGTTAATGGTGAT TTTACATTGTTATGTTACCACGATTTGTAAAAGAGCAGCTGCGCTGAGAATGAGCATGCTT GTCATTGGCAGCTCTCTGAGATTTTCAGTGCCTCTTACTGGCTTGTTAAGAAGACGCCAAAA

Page 186 of 359

53/246

FIGURE 52

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA129580
><subunit 1 of 1, 114 aa, 1 stop
><dw: 12886, pi: 7.04, Nx(s/t): 0
MQIQNNLFFCCYTVMSAIFEWELLYSLPALCFLLGTQESESFHSKAEILVTLSQVIISPA
GPHALTWTHFSPSVIILUPFCWHADVITVOHPVANCYVTNHLNIOWLELKAGS

Important features of the protein:
Signal peptide:
Amino acids 1-33

WCG268268 [He://E./W/06266286 opc]

Transmembrane domain: Amino acids 71-86

N-myristoylation site: Amino acids 35-41

Page 187 of 359

WC0268268 [Be://E_W/06206286 opc]

54/246

FIGURE 53

TTTTGAAATGGTTT**ATG**ACCTCTTCCCCACTTCCCCGCTTGCTTTGCTCATTAGTGTTCCTA GGTGGCTGCTGGGTGACGGGCTTTTCATCATCTCTGATGTGGGCCAGTGCGAAAGAGCAGCT GCAACATCTGTTTCTAATTGGGTCGTGCCTTTATAAATACTTCTTGCCTATTTGTCACATTG CTTCCCTCCCACCCTGTCTTCCTTGGAGTACTGCAGAATCTGTAAGCGTCCCTGGAATGCAC ACGTGGACCTTGTCATTCCCAAACAGACTTTCTGCTGGTCAGCACTTTGTAATGTTCGGCTG TTACAGGCATTAGTCACTTGTGCTCAGAGAGAGACTGTGGTCTTTGGAAACTGAAGAAATGTC TTTTTTGTTGTTAATTCTTGGCATCCAGTTAGATTTAACTTCTCAAGAGTTTACACAGA CTTTTAGAAAAACATTCTGTCTCTAAGAAAAAGTGCTCTAGCTTTGTACAGTTTTTGGATT TTCACACTTGGTGGTTGTTTGCTGAAATGCTGTTTTGCTAGTGATTCCCCTCCTCCCCCTAT CTGGGGTTGTAAGCAGCTCTGGGGCTCTGTTCACTTCGGATACCTGTTTCTGGGGACTGCTT TTCAACAGCGTTTTTCCTAAGGGCATATGAGAAATTTAATTTCTGATGGAATGAAGGTGAAA CTCTAGTCCCAGGTAAACCTGGGTAGGCTGTAGAGACAGAAAGGGGGCTGCAGGTCTAGGTG GAAGAACGAGAACGAATGCAGCATGGTATTTCCAGGCCTTTTAGATTCGGCTTCATCCACAA CCAATGTGAGTTCTTATCTGCAAAGCGGGCCTAAGTGTAATGGAGGGAAGGTGGGCCAGGCA CCAGGGTCCTGGGTTCTCCCGCGCCTCACTCTGTCTCCACCTGGCCCATGCATAAAGAACAC TAGTCAAGTAGCCATTGTACCTGTTTCCTTATCTGAAAATGAGAAGGTTGGAGAGTATGACT TCTGTTGAAACAACAAGGCGCTTACAAATTTTGGTGAAGTCGAATGAGGGCAGCGTTAAGAG AAATATCAAAGTTAGTCATTGGATTTCAGGGCTTAGGGATGGAAACCAGCTGGTAGTAGACT ACCAGCAAATGTTAGAGGTATACATCAGGGCACAGAGGAGAAAAGCTAACATGATACTGATG ACTTCAAGTCTTCACTGTCCAATTCAGAGGATAGGGGAGGGTTTAAGCTGATTAAACAGTGG TAATACATGTTATTCTGGGGGGACTCTCTTATACCTTGAAGTAGACATTGCTGCTATTTGCGT GAAAAAAATAGGAGGACTTATTTGAATTGAGAATGGGGATAGGCTGAGTTCCACCGAGATGT TGGCTTAGAGATGCCTGGGCCATGCTGTACAGTAGGAAGCCCAGCAGAGGAGATTGGGCTGT GTGGGTCATGACAAAGGGAGTTGTTAGCTTATGGTTGGCTATTAAAGTCATGGGCAAGGATG GGCAAGAAAGTGTGTAAAATGAGCTGACAAAAGATAAATATGTTAATTA

Page 188 of 359

55/246

FIGURE 54

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA129794 ><subunit 1 of 1, 102 aa, 1 stop ><dW: 11382, pI: 8.72, NX(5/T): 0 MTSSPLPRLICSLYFLGGCWYTGFSSSLMWASAKEQLOHLFLIGSCLYKYFLPICHIASL PPCLPWSTAESVSYPGHTWTLSFPNIKJAGOHFWTGCYRH

Important features of the protein: Signal peptide: Amino acids 1-21

N-myristoylation site: Amino acids 18-24

WCG208268 [Re://E/W/00206286 opc]

Drokementic members lines

Prokaryotic membrane lipoprotein lipid attachment sites: Amino acids 9-20;36-47; 89-100

Page 189 of 359

WC0268268 [like://E_W/06206286 opc.]

WO 02/08288 PCT/US01/21066

56/246

FIGURE 55

ACACTGGCCAAACACTCGCATCCCAGGGCGTCTCCGGCTGCTCCCATTGAGCTGTCTGCTCG GGAGACGCCAGCGAGCTGGTGATTGGAGCCCTGCGGAGAGCTCAAGCGCCCAGCTCTGCCCG AGGAGCCCAGGCTGCCCCGTGAGTCCCATAGTTGCTGCAGGAGTGGAGCCATGAGCTGCGTC CTGGGTGGTGTCATCCCCTTGGGGCTGCTGTTCGTGGTCTGCGGATCCCAAGGCTACCTCCT GCCCAACGTCACTCTCTTAGAGGAGCTGCTCAGCAAATACCAGCACAACGAGTCTCACTCCC GGGTCCGCAGAGCCATCCCCAGGGAGGACAAGGAGGAGATCCTCATGCTGCACAACAAGCTT CGGGGCCAGGTGCAGCCTCAGGCCTCCAACATGGAGTACATGACCTGGGATGACGAACTGGA GAAGTCTGCTGCAGCGTGGGCCAGTCAGTGCATCTGGGAGCACGGGCCCACCAGTCTGCTGG TGTCCATCGGGCAGAACCTGGGCGCTCACTGGGGCAGGTATCGCTCTCCGGGGTTCCATGTG GTGTCCAGAGAGGTGCTCGGGGCCTATGTGCACGCACTACACAGATAGTTTGGGCCACCA CCAACAAGATCGGTTGTGCTGTGAACACCTGCCGGAAGATGACTGTCTGGGGAGAAGTTTGG GAGAACGCGGTCTACTTTGTCTGCAATTATTCTCCAAAGGGGAACTGGATTGGAGAAGCCCC CTACAAGAATGGCCGGCCCTGCTCTGAGTGCCCACCCAGCTATGGAGGCAGCTGCAGGAACA GAAACGGCTCCCATTCCTGAAGAAAACCATGTTTGGCTCCAACCGAGGGTGATGAGACCCAC CAAGCCCAAGAAAACCTCTGCGGTCAACTACATGACCCAAGTCGTCAGATGTGACACCAAGA TGAAGGACAGGTGCAAAGGGTCCACGTGTAACAGGTACCAGTGCCCAGCAGGCTGCCTGAAC CACAAGGCGAAGATCTTTGGAAGTCTGTTCTATGAAAGCTCGTCTAGCATATGCCGCGCCGC CATCCACTACGGGATCCTGGATGACAAGGGAGGCCTGGTGGATATCACCAGGAACGGGAAGG TCCCCTTCTTCGTGAAGTCTGAGAGACACGGCGTGCAGTCCCTCAGCAAATACAAACCTTCC AGCTCATTCATGGTGTCAAAAGTGAAAGTGCAGGATTTGGACTGCTACACGACCGTTGCTCA GCTGTGCCCGTTTGAAAAGCCAGCAACTCACTGCCCAAGAATCCATTGTCCGGCACACTGCA AAGACGAACCTTCCTACTGGGCTCCGGTGTTTGGAACCAACATCTATGCAGATACCTCAAGC ATCTGCAAGACAGCTGTGCACGCGGGAGTCATCAGCAACGAGAGTGGGGGTGACGTGGACGT GCCTGGGGACTCCTCGGGATGGAAAGGCCTTCCGGATCTTTGCTGTCAGGCAGTGAATTTCC GTCATTGCGGGGTATATGGAGAGTCA

WC0008088 His/ME/W00008289 opc| Page | 170 od 55%

PCT/US01/21066

57/246 FIGURE 56

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA131590

><subunit 1 of 1, 497 aa, 1 stop

><MW: 55906, pI: 8.43, NX(S/T): 4

MSCVLGGVI PLGLIFIVGGSGGYLLFNVTLLEELLSKYQHNESHSRVRRAI PREDKEE IL MHINKLRGGVOPQASNMEYMTWDDELEKSAAAWASQCI WEHEGPTSLLVSIGGNLGAHWGR YRSPGHVOSWYDBVKDYTYPYBSCNPWCPERCSGPMCTHYTOIVWATTNKIGGAVNTC RKMTVWGEVWENAVYFVCNYSPKGNWIGEAPYKNGRPCSECPPSYGGSCRNNLCYREETY TFKPETDEMNSVETAPI PEENHWULQFRVMRFTKFKKTSAVNYMTQVVRCDTKMKDRCKG STCNRYQCPAGCLHKKAKIFGSLFYESSSSICRAAIHYGILDDKGGLVDITRNGKVPFFV KSERHGVGSLSKYKFSSSFWYSKVKVQDLDCYTTVAQLCPFKFRATHCFRIHCPAHCKDE PSYWAPVFGTNIYADTSSICKTAVHAGVISNESGGDVDVMPVDKKKTYVGSLRNGVQSES LGTPRDGKAFRIFFAVRO

Important features of the protein:

Signal peptide:

WO 02/08288

Amino acids 1-22

N-glycosylation sites:

Amino acids 27-31;41-45;451-455

cAMP- and cGMP-dependent protein kinase phosphorylation sites: Amino acids 181-185;276-280;464-468

Tyrosine kinase phosphorylation site:

Amino acids 385-393

N-myristoylation sites:

Amino acids 111-117;115-121;174-180;204-210;227-233;300-306;

447-453;470-476

Extracellular proteins SCP/Tpx-1/Ag5/PR-1/Sc7 signature 2:

Amino acids 195-207

SCP-like extracellular protein:

Amino acids 56-208

WCG298268 [Ne://E/W/29206286 opc.]

WO 02/08288

PCT/US01/21066

Page 171 of 359

58/246

FIGURE 57

Page 172 of 359

WCG268268 [Re://E/W/06266286 opc]

59/246

FIGURE 58

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA135173
><subunit 1 of 1, 93 aa, 1 stop
><dw: 10456, pi: 4.37, Nx(s/T): 1
MKVVMVLLLAALPIYCYAGSGCVLLESVVEKTIDFSVSVEEYKADLQRFIDTEQTEAAVE
EFKECTLSCNSETLANFRWYHTIYDSJLYCAAY

Important features of the protein: Signal peptide: Amino acids 1-18

Prokaryotic membrane lipoprotein lipid attachment site: Amino acids 12-23

Page 173 of 359

60/246

WC0268268 [like://E_W/06206286 opc.]

FIGURE 59A

CAAGTCCGTTGAGGCTGCCAGGCGAGTCAGGTCTCTCTGGACCTCGCCTGACTCGGCTGGGC TGTGCCTGAAATTGACCCAGCTCCACCATACTCCTTGATTATGAGAAAACAAGGAGTAAGCT CGGGAGCCGGAGGTAGAGGAGGAGGTGGAAAAGTCGGTCCTAGGCGGCGGGAAACTGCCAAG GGGCGCCTGGAGGTCCTCCCCGGGGAGGATCCAAAGTCTGAAAGAGCGAAAAGGCTTGGAGC TAGAGGTGGTGGCCAAGACCTTTCTTCTCGGCCCCTTCCAGTTCGTCCGTAATTCCCTGGCG CAGCTCCGGGAAAAGGTGCAGGAACTGCAGGCGGCGGTTCTCCAGCAGAACCACTCTCGG CATCGCTGTCTTTGTGGCAATTTTACATTGGTTACATTTAGTAACACTTTTTGAAAATGATC GTCATTTCTCTCACCTCTCATCTTTGGAACGGGAGATGACTTTTCGCACTGAAATGGGACTT TATTATTCATACTTCAAGACCATTATTGAAGCACCTTCGTTTTTGGAAGGACTGTGGATGAT CTAGAAACTAAGACCTGCTGGAATGTCACCAGAATAGAACCTCTTAATGAAGTTCAAAGCTG TGAAGGATTGGGAGATCCTGCTTGCTTTATGTTGGTGTAATCTTTATTTTAAATGGACTAA TGATGGGATTGTTCTTCATGTATGGAGCATACCTGAGTGGGACTCAACTGGGAGGTCTTATT ACAGTACTGTGCTTCTTTTCAACCATGGAGAGGCCACCCGTGTGATGTGGACACCACCTCT CCGTGAAAGTTTTTCCTATCCTTTCCTTGTACTTCAGATGTGTATTTTAACTTTGATTCTCA GGACCTCAAGCAATGATAGAAGGCCCTTCATTGCACTCTGTCTTTCCAATGTTGCTTTTATG CTTCCCTGGCAATTTGCTCAGTTTATACTTTTTACACAGATAGCATCATTATTTCCCATGTA TGTTGTGGGATACATTGAACCAAGCAAATTTCAGAAGATCATTTATATGAACATGATTCAGTT ACCCTTAGTTTCATTTTGATGTTTGGAAATTCAATGTACTTATCTTCTTATTATTCTTCATC TTTGTTAATGACGTGGGCAATAATTCTAAAGAGAAATGAAATTCAAAAACTGGGAGTATCTA AACTCAACTTTTGGCTAATTCAAGGTAGTGCCTGGTGGTGGGAACAATCATTTTGAAATTT CTGACATCTAAAATCTTAGGCGTTTCAGACCACATTCGCCTGAGTGATCTTATAGCAGCCAG AATCTTAAGGTATACAGATTTTGATACTTTAATATACCTGTGCTCCCGAATTTGACTTCA TGGAAAAAGCGACTCCGCTGAGATACACAAAGACATTATTGCTTCCAGTTGTTATGGTGATT ACATGTTTTATCTTTAAAAAGACTGTTCGTGATATTTCATATGTTTTAGCTACAAACATTTA TCTAAGAAAACAGCTCCTTGAACACAGTGAGCTGGCTTTTCACACATTGCAGTTGTTAGTGT TTACTGCCCTTGCCATTTTAATTATGAGGCTAAAGATGTTTTTGACACCGCACATGTGTGTT GAAGGTTATCTTTGGCATTTTAACAGTGATGTCAATACAAGGTTATGCAAACCTCCGTAATC AATGGAGCATAATAGGAGAATTTAATAATTTGCCTCAGGAAGAACTTTTACAGTGGATCAAA TACAGTACCACATCAGATGCTGTCTTTGCAGGTGCCATGCCTACAATGGCAAGCATCAAGCT GTCTACACTTCATCCCATTGTGAATCATCCACATTACGAAGATGCAGACTTGAGGGCTCGGA CAAAAATAGTTTATTCTACATATAGTCGAAAATCTGCCAAAGAAGTAAGAGATAAATTGTTG GAGTTACATGTGAATTATTATGTTTTAGAAGAGGCATGGTGTTGTGAGAACTAAGCCTGG GTAGCGTCCTGCTCGAAGACGCCAGGCCTTACTTCACCACAGTATTTCAGAATAGTGTGTAC AGAGTATTAAAGGTTAACTGAGAAGGATACTACCCATTTTACTATGGCACAATGCCGTGTGT CAAAAACAATCACCCTTTGGCTTATTCACATTAATAAAAATCACAAGCTTTAATAACAGACA CTTAAAAATAAGATAAAAATGGATTGGAAATTTTTCTGATTACTAAAAGGTAAATTACTTTT ACTGCATAAACAAATGTTCATTTCAGAATTTTAAAGAGAAATGTATATAAAGAACMATGATT TTAATAATCAGGGGTATGTAAGTCCTTTTTCATCCAACTAGGTGAATTGCTTCAGATTTTCT CTAGTACCAGAGGGTACCTCCTCAAACTCTTTGAACCACTTAAGGCAGAAGAATGCAAGCTC TGAAATGACATCCTTAAAATGCTGATACTGGTCACAGCCTCTTTACCTCTGTGAGGAAATTG TTTAATACTTTTTTTTAATAATTTCAAGTTGAAGTGTTTTTAAAAACACTTTGTTTTGTAAT GTTTTGAATCTCTTGAGATGTGTTTACCCCACTAGATACATATTTGCCACTGGTTAGTTCTC CATCTAAGCTCAAGAGGTTATTCATCTCTCTTTAGATTCCAGTGGCTTTTCTTTTAACATCC AGGTAAAACAGAAACTGCTATGGTATACAACCAAGTTTTGGGGTTAAACATAATCAGAAAAG

Page 174 of 359

WO 02/08288

61/246

FIGURE 59B

Page 175 of 359

62/246

FIGURE 60

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA138039

><subunit 1 of 1, 758 aa, 1 stop

><MW: 87354, pI: 9.36, NX(S/T): 1

MRKQGVSSKRLQSSGRSQSKGRRGASLAREPEVEEEVEKSVLGGGKLPRGAWRSSPGRIQ
SLKERKGLELEVVAKTFLLGPFQFVRNSLAQLEEKVQELQARRFSSRTTLGIAVFVAILH
WLHLYTLENDRHSHLSSLEREMTFRTEMGLYYSYFKTIIEAPSFLEGLWMIMDRLTE
YPLIINAIKRFHLYPEVIIASWYCTFMGIMNLFGLETKTCMNVTRIEPLNEVQSCEGLGD
PACFFYGVIFINGLMWGLFFMYGAVLSGTQLGGLITUTLCFFFHAGATRVMMTPPLRES
FSYPFLVLQMCILTLILRTSSNDRRPFIALCLSNVAFMLPWQFAQFILFTQIASLFPMYV
VGYIEPSKFQKIITMNMISTLFSILMFGONSWYLSSYYSSSLLMTWAIILKRNEIQKLGV
SKLNFWLLQGSAWMGGTIILKFLTSKLGVSDHIRLSDLIAARILRYTDFDTLIYTCAPE
FDFMEKATPLRYTKTLLLPVMVNITCFIFKKTVRDISVYLATNIYLRKQLLEHSELAFHT
LQLLVFTALAILIMRLKMFLTPHMCVMASLICSRQLFGWLFRRVRFEKVIFGILTVMSIQ
GYANLRNGWSIIGEFNNLPQEBLLQHIKYSTTSDAVFAGAMPTMASIKLSTLHPIVNHPH
YEDADLRARTKIVYSTYSRSAREVROKKLELHVNYYVLEEBAWCVVRTKPGCSMLEIWDV
EDDSNAAMPPLCSVLLEDARPYFTTVFONSVYRLKKN

Important features of the protein:

Transmembrane domain:

WO0268268 [He://E-/W/00206286 opc]

Amino acids 109-124;197-213;241-260;266-283;302-315;336-356; 376-391;430-450;495-509;541-560;584-599;634-647

N-glycosylation site:

Amino acids 222-226

cAMP- and cGMP-dependent protein kinase phosphorylation site: Amino acids 102-106

Tyrosine kinase phosphorylation site:

Amino acids 511-519

N-myristoylation sites:

Amino acids 24-30;50-56;151-157;254-260;264-270;269-275;

273-279;639-645

Amidation site:

Amino acids 20-24

Page 176 of 359

63/246

WC0268268 [Be://E_W/06206286 opc]

FIGURE 61

GGCGCGCCACATCCTTTAAATATGGTCTTTCTTGGGCGCGCGACAATGTGAGGAGTGGG GTGGAGCGTGTGTGTGTGTGCTGCGCCTGGGCAAGAGCCGCCGCGGACCATGAGCTGAG TAGAGTGAAGCAGAAATCTAGGAAGATGAGCTCCAAGATGGTCATAAGTGAACCAGGACTGA ATTGGGATATTTCCCCCAAAAATGGCCTTAAGACATTTTTCTCTCGAGAAAATTATAAAGAT CATTCCATGGCTCCAAGTTTAAAAGAACTACGTGTTTTATCCAACAGACGTATAGGAGAAAA AGGAAAAGTTAAAACCACAATTGGAATGGTTCTTCTTCCAAAACCAAGAGTTCCTTATCCT CGTTTCTCTCGTTTCTCACAGAGAGCAGAGGAGTTATGTGGACTTGTTGGTTAAATACGC ATATGAAAAAACATGTGAACGAAGAAGTTACTGAGTTCCTAAAGTTTTTTGCAGAATTCTGCA AAGAAATGTGCGCAGGATTATAATATGCTTTCTGATGATGCCCGTCTCTTCACAGAGAAAAT TTTAAGAGCTTGCATTGAACAAGTGAAAAAGTATTCAGAATTCTATACTCTCCACGAGGTCA CCAGCTTAATGGGATTCTTCCCATTCAGAGTAGAGATGGGATTAAAGTTAGAAAAACTCTT CTCGCATTGGGCAGTGTAAAATATGTGAAAACAGTATTTCCCTCAATGCCTATAAAGTTGCAG CTGTCAAAGGACGATATAGCTACCATTGAAACGTCAGAACAACAGCTGAAGCTATGCATTA TGATATTAGTAAAGATCCAAATGCAGAGAAGCTTGTTTCCAGATATCACCCTCAGATAGCTC TAACTAGTCAGTCATTATTTACCTTATTAAATAATCATGGACCAACGTACAAGGAACAGTGG GAAATTCCAGTGTGTATTCAAGTAATACCTGTTGCAGGTTCAAAACCAGTTAAAGTAATATA AAGTTCCATTAAAATTTATGATGTCCAAAAACACATCTGTTCCAGTCTCTGCAGTCTTTATG GACAAACCTGAAGAGTTTATATCTGAAATGGACATGTCCTGTGAAGTCAACGAGTGCCGAAA AATTGAGAGTCTTGAAAACTTGTATTTGGATTTTGATGATGTCACAGAACTTGAAACTT TTGGAGTAACCACCACAAAGTATCAAAATCACCAAGTCCAGCAAGTACTTCCACAGTACCT AACATGACAGATGCTCCTACAGCCCCCAAAGCAGGAACTACAACTGTGGCACCAAGTGCACC AGACATTTCTGCTAATTCTAGAAGTTTATCTCAGATTCTGATGGAACAATTGCAAAAGGAGA AACAGCTGGTCACTGGTATGGATGGTGGCCCTGAGGAATGCAAAAATAAAGATGATCAGGGA TTTGAATCATGTGAAAAGGTATCAAATTCTGACAAGCCTTTGATACAAGATAGTGACTTGAA AACAT CTGATGCCTTACAGTTAGAAAATTCTCAGGAAATTGAAACTTCTAATAAAAATGATA TGACTATAGATATACTACATGCTGATGGTGAAAGACCTAATGTTCTAGAAAACCTAGACAAC TCAAAGGAAAAGACTGTTGGATCAGAAGCAGCAAAAACTGAAGATACAGTTCTCTGCAGCAG TGATACAGATGAGGAGTGTTTAATCATTGATACAGAATGTAAAAAAACCAGTTATAACAGTG TTTAATTTAGATAAGTTTGAGGGAAAATAATCAGTAGGCAAGAGGAACATTTTTCCTGTAGT AGCTAGAGTGCCTTGAAAAATGTGTTGGCTATGTGAAGGAATATTTCAACTAAAATGGAAT GGTATGCTTTTCACCCTTAAAGTTTGAGGAGGATCTTGATATGTTTTAACATTATCATGGCA GGGAAATATATAAAGAAGAAAAATATTTTTACATTAAACCTTTTCTAAAAATTGTAAATAGA CCAGTCTGTTGCGACTGACTCAAAAAGTTAAATGTTGCCACTGCTGAAGATGATTATGAGCA TCGCAAACTTTGTTTCTGACCCATTTTGACAGTTTTTATATACTCCTTTAAAATGATGAATG TTACAGGTTAATAAAGTTAATACCTTTAAA

Page 177 of 359

64/246

FIGURE 62

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA139540
><subunit 1 of 1, 592 aa, 1 stop
><MW: 66453, pI: 5.42, NX(S/T): 3</pre>

MSSKMVISPCINWDISPKNCLKTFFSRENYKDHSMAPSLKELRVLSNRRIGENLNASAS
SVENEPAVSSATQAKEKVKTTIGMVLLPKFRVPYPRFSRFSQREQRSYVDLLVXAKIPA
NSKAVGINKNDYLQYLDMKKHVNEEVTEFLKFLQNSAKKCAQDYNNLSDDARLFTEKILR
ACIEQVKKYSEFYTHBVTSLMGFFFFRVEMGLKLEKTLLALGSVKYVKTVFFSWFIKLQ
LSKDDIATIETTSEQTABAMHYDISKDPNAEKLVSRYHPQIALTSQSLFTTLINNHGFTYKE
QWEIPVCIQVIPVAGSKPVKVIYINSPLPQKKMTMRERNQIFHBVPLKFFMSKNTSVPVS
AVFMDKPEEFISEMDMSCEVNECKKIESLENLYLDFDDDVTELETFGVTTTKVSKSPSPA
STSTVPNMTDAPTAPKAGTTTVAPSAPDISANSRSLQILMEQLQKEKQLVTGMOGGPE
CKNKDDQGFESCEKVSNSDKPLIQDSDLKTSDALQLENSQBIETSNKNDMTIDILHADGE
RRVVLENLDNSKEKTVGSEAAKTBDTVLGSSDTDEBCLIIDTECKKTSYNSV

Important features of the protein: N-glycosylation sites:

Amino acids 56-60;354-358;427-431

cAMP- and cGMP-dependent protein kinase phosphorylation sites:
Amino acids 187-191;331-335;585-589

N-myristoylation sites:

WC0268268 [Be://E-W/00206286 opc]

Amino acids 126-132;407-413;557-563

Page 178 of 359

WC6268368 (Her//E/W/06266286 opc)

WO 02/08288 PCT/US01/21066

65/246

FIGURE 63

TTTTTAACTTGAACTTCCAAGGCCACGTGCGTCTCCTGGCTCCTGCACGGACTGTGTGACTG TCCCCGACAGCTTTCCTGTCTCGTCTCATGAGGGGTCCAGCACATGGCATTCTGGGTCGGCA CCTGAAGTCCACCTCTATGAGACCCTCTGGGAGCGTGACGGGCCTTGGCATGGGTCGGCCG AGGCCCTTCTGTCCCAGGTCACTGGTGTGGTCGGCCCAGGCCCTCCTGTCCCACATCACCTG TGTGGTCGGCCCAGGCCCTCTGTCCCAGGTCACCGGTGTGGTCGGCCCAGGCCCTCCTGTC CAGGTCCTCCTGTCCAGGTCACTGGTGTGGTCGGCCCAGGCCCTTCTGTCCCAGGTCACCTG CAGGGACTTGGCATTGGTGGGGCAGGGTTCCAAGGTGTGGCCTGTCAGCAGGAAGGGGCAG GTGGCATGGGTCCAGGCGGGACTCAGGGCTGGGGTGCCACTGCTGGAGACTGTCCGGAGGCC CCTCCAGGGCACCTTGCCATTGCCATTGTCGCTCATGGCCATCTGGTCCCGTTTCAGGGAAC AAGAGGAGGATCAGATGCTGCGGGACATGATTGAGAAGCTGGGTGACTGGGCCGGGGATGCT GGACCGGGCCTCCAGCTGGGGGGGGGGGGGGGGGGTATCGGGTCCCCCCTCAGCCTTGG GGCAGCTGGTGACCGTGTGGTCATGGTGGGGACCAGCCCTCCGGGGCACCCAGTCGGGGCAG GTTCTCACGTGGGAGGCCACAGGCTTCCTGCAGGCTCGGAGGCCCAGGGCGGATTGTGGCC AGTGGAAGGGAAGGATGTTTCTGGCAGGGGGACTTGTGTGGGCCACGGCTGTGCGGCTGCGG CGTTGAGCACGGCCTCACTGTCCACCTGTCCCCTAGGCCTCCAGAGGAAGAAGTCCAAGTTC CGCTTGTCCAAGATCTGGTCACCAAAAAGCAAAAGCACCCCTCCCAGTAGTAGCCAGTAGG GCCGTGGGCTCGGCCCGGACCTGGCATCCGGACTTGGACTCGGGGCCATGGGCTTGGCCCGG ACCCGGAACCCGGACTTGTACTCGGGCCGTGGGCTCGGCCCGGACCCGGCATTCGGACTTG GACTCGGGAAGGGCCTCCTGTCCCTACAAGGGGCATGTGGACAGCAGGGACCTGCGCTACCG AAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

WC0008088 (Ne // E Av 00000838 opc.)

WO 02/08288 PCT/US01/21066

66/246

FIGURE 64

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA139602 ><subunit 1 of 1, 159 aa, 1 stop >KMW: 15900, pI: 8.07, NX(s/T): 0 MGRPRPFCPRSLVWSAQALLSHITCVVGPGPPVPGHRCGRPRPSCPGPPVQVTGVVGPGP SVPGHLCGRPRALLYHYTVBGLALEBGRDLALVGAGFQGVACQQEGAGGMGPGGTQGWGA TAGGCPEAPPGHLATAVHGHLVPFOGTRGGSDAAGHD

Important features of the protein: Signal peptide: Amino acids 1-25

N-myristoylation sites:

Amino acids 109-115;113-119;119-125;148-154;151-157;152-158

Page 180 of 359

67/246

WC0268268 [like://E_W/06206286 opc.]

FIGURE 65

GGCGACCACCGCCGCCTCCTCACCTGGCCATTGGTGCAGCCCGTTCCCGGCGGCGAGAGAAG GCAGGCGCCCCTTGCGCCACGCCACACCGTCGGGCCCCCGTCGGGTCCCCCTCGGGCCGCA ATGGTGGGCTCCGCGCGGCTCCGGCACTCTTGACCCCCTTTGTAACCACCGCGGCGGG CACCCAGGGAGTTCGAGCAACGAAGTTGGTGACCTGCCCCGCTCCCAGGCAGTTTGCTGTTG GGGCTTTCACGGCTGCTGGAAGGGCATGGCTGTTTGTCCCATCACTGGGCGCCAGCTTCTCA AAGCTACGTTCACAGCAACGCAGTAGGGACTTTCGTGGCAGGCTTTTTTTAAGAGCTGAAAG AAGGGCGGAGGGTTTACGTCCTAGGGTGATGATTTCCTCACCAGACAGCGAAGTATCTATT GGGAAACTCCAGGTGACCGCACCTCCTTCCGACAGTTCGCCCCGGGGCAAGTTTACCAGCTG CGTCAGAAAGCAGGTTTGCAAAATCCTTGGAGAACGGCCTGAGCTAAGGACTGGGGTCAGGA GGGTTTTAAACTCATTCTGATTTTCTTGCAATCATATCTCTTGAAAGTTTTTATATTTTCCC CAATATTTTTCTGAGTTGCTATATCCAATGAAAACAATGCTGATGTAGAGGTCCACCAGCCA GAATGTGAACCTCTTCCAAGGTCTGGGCGAGTCCCTAGAGTTACGCAGATGAAGGACATTGG CCCTCGAGAATCTCACACCAGCAAAGAAGAGCACAACGAAGCGCAAACTACTTATGATCATT GTGGCTTTGGGCAAGTTGTTGTAGCTCCCAGCAACAATTTCTTCACCTGGAGTGCAGCAATA AATGATACTGGTGCTGCAGGGCAGCTAATAAGCTTCTGAATAATATATGCAAAGTACTTGGC ACCATGAGCAGAACTCAGTATACCGTCACTGAAGAAATAGCTTATTTAATGATTACACTTTT CATATGTGCAAGTAAAAGTTTGACTTTTAGGGAGGCCTCACCTACGGAATGTCTTTTTTAA ATTTCTTTTTAATTATACTTTAAGTTCTGGGATACATGTGCAGAACGTGCAGGTTTGTTAC ACAGGTATACATGTGCCATGGTGGTTTGCAGCACCCATCAACCCTTCATCTAGGTTTTAAGC TCCGCATGCATTAGTTATTTGTCCTAATGCTCTCCCTTCCCCTTGTCCCCCACCCCCCAACAG GCCTCAGGGTGTGATGTTCCCCTCCCTGGGTCCATATGTTCTCATTGTTCAACTCCCACTTA TGATGAGAACATGCAGTGTTTGGTTTTCTGTTCCTGTGTTAGTTTGCTGAGAATGATGGTTT TCCATGGTGTATATGTGCCACATTTTCTTCATCCAGTCTATCATTGATGGGCACTTGGGTTG GTTCCAAGACTTTGTTATTGTGAACAGTGCTGCAATAAACATACGTTTGTATGTGTCAAAAA AAAAAAAAAAAAAA

Page 181 of 359

WCG298268 [Ne://E/W/29206286 opc.]

68/246 FIGURE 66

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA139632 ><subunit 1 of 1, 90 aa, 1 stop ><MW: 9586, pI: 12.18, NX(S/T): 0 MVGSARLGPALLTPFVTTAAGTQGVRATKLVTCPAPRQFAVGAFTAAGRAWLFVPSLGAS FSKLRSOORSRDFRGRLFLRAERRAGGFTS

Important features of the protein: Signal peptide: Amino acids 1-24

N-myristoylation sites: Amino acids 24-30;42-48;58-64

Page 182 of 359

WC0268268 [like://E_W/06206286 opc.]

69/246

FIGURE 67

CATGTCTAGACTGGGAGCCCTGGGTGGTGCCCGTGCCGGGCTGGGACTGTTGCTGGGTACCG CCGCCGGCCTTGGATTCCTGTGCCTCCTTTACAGCCAGCGATGGAAACGGACCCAGCGTCAT GGCCGCAGCCAGAGCCTGCCCAACTCCCTGGACTATACGCAGACTTCAGATCCCGGACGCCA CGTGATGCTCCTGCGGGCTGTCCCAGGTGGGGGCTGGAGATGCCTCAGTGCTGCCCAGCCTTC CACGGGAAGGACAGGAGAGGTGCTGGACCGCCTGGACTTTGTGCTGACCAGCCTTGTGGCG $\tt CTGCGGCGGGAGGTGGAGGGCTGAGAAGCAGCCTGCGAGGGCTTGCGGGGGAGATTGTTGG$ GGAGGTCCGATGCCACATGGAAGAGCCAGAGAGTTGGCTCGGCGGCGAAGGTTTCCGTTTG TCCGGGAGAGGAGTGACTCCACTGGCTCCAGCTCTGTCTACTTCACGGCCTCCTCGGGAGCC ACGTTCACAGATGCTGAGAGTGAAGGGGGTTACACAACAGCCAATGCGGAGTCTGACAATGA GCGGGACTCTGACAAGAAGTGAGGACGGGGAAGATGAAGTGAGCTGTGAGACTGTGAAGA TGGGGAGAAAGGATTCTCTTGACTTGGAGGAAGAGGCAGCTTCAGGTGCCTCCAGTGCCCTG GAGGCTGGAGGTTCCTCAGGCTTGGAGGATGTGCTGCCCCTCCTGCAGCAGGCCGACGAGCT GCACAGGGGTGATGAGCAAGGCAAGCGGGAGGGCTTCCAGCTGCTCAACAACAAGCTGG TGTATGGAAGCCGGCAGGACTTTCTCTGGCGCCTGGCCCGAGCCTACAGTGACATGTGTGAG CTCACTGAGGAGGTGAGCGAGAAGAAGTCATATGCCCTAGATGGAAAAGAAGAAGCAGAGGC TGCTCTGGAGAGGGGGATGAGAGTGCTGACTGTCACCTGTGGTATGCGGTGCTTTGTGGTC AGCTGGCTGAGCATGAGAGCATCCAGAGGCGCATCCAGAGTGGCTTTAGCTTCAAGGAGCAT GTGGACAAAGCCATTGCTCTCCAGCCAGAAAACCCCATGGCTCACTTTCTTCTTGGCAGGTG GCCCTCTCAGTGCCACTGTGGAAGATGCCCTCCAGAGCTTCCTAAAGGCTGAAGAACTACAG CCAGGATTTTCCAAAGCAGGAAGGGTATATTTTCCAAGTGCTACAGAGAACTAGGGAAAAA CTCTGAAGCTAGATGGTGGATGAAGTTGGCCCTGGAGCTGCCAGATGTCACGAAGGAGGATT TGGCTATCCAGAAGGACCTGGAAGAACTGGAAGTCATTTTACGAGACTAACCACGTTTCACT CTTGCTGAGATCAGGAAACCACACACATCTGTCTCCTGGGTCTGACTGCTACCCACTACCAC TCCCCATTAGTTAATTTATTCTAACCTCTAACCTAATCTAGAATTGGGGCAGTACTCATGGC TTCCGTTTCTGTTGTTCTCCCCTTGAGTAATCTCTTAAAAAAATCAAGATTCACACCTGCC CCAGGATTACACATGGGTAGAGCCTGCAAGACCTGAGACCTTCCAATTGCTGGTGAGGTGGA TGAACTTCAAAGCTATAGGAACAAAGCACATAACTTGTCACTTTAATCTTTTTCACTGACTA GAGTGGCCCACAGACATTGCTTTCTTATCACCTATCATGTGAATTCTACCTGTATTCCTGGG CTGGACCACTTGATAACTTCCAGTGTCCTGGCAGCTTTTGGAATGACAGCAGTGGTATGGGG TTTATGATGCTATAAAACAATGTCTGAAAAGTTGCCTAGAATATATTTTGTTACAAACTTGA AATAAACCAAATTTGATGTT

Page 183 of 359

70/246

FIGURE 68

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA139686

><subunit 1 of 1, 470 aa, 1 stop

><MW: 52118, pI: 5.06, NX(S/T): 0

MSRLGALGGARAGIGILLIGTAAGLGFLCLLYSORWKRTORHGRSQSLPNSLDYTOTSDFG
RHVMLIRAVFGGAGDASVLPSLPREGQEKVLDRLDFVLTSLVALRREVEELRSSLRGLAG
EIVGEVRCHMEENGRVARRRRFFFVEERSDSTGSSSVYFTASSGATFTDAESEGGYTTAN
ASSDBERDSDKESEDGEDEVSCETVKMGRKDSLDLEEEAASGASSALEAGGSSGLEDULP
LLQQADELHRGDEGGKEEGFQLLLNWKLYVGSROPFURLRARYSDMCELTEEVSEKKSY
ALDGKEEAEAALEKGDESADCHLWYAVLCGQLAEHESIQRRIQSGFSFKEHVDKAIALQP
ENPMAHFLLGRWCYQVSHLSWLEKKTATALLESPLSATVEDDALQSFLKAEELQPGFSKAG
RYYISKCYRELGKNESARWWMKLALELDPDYTKEDLAIOKDLEELEVILRD

Important features of the protein:

Signal peptide:

WCG268268 [IB#7/E-AV-06206286 opc.]

Amino acids 1-32

cAMP- and cGMP-dependent protein kinase phosphorylation site: Amino acids 209-213

N-myristoylation sites:

M Myllacoylacion sices.

Amino acids 5-11;8-14;9-15;15-21;19-25;72-78;164-170; 174-180;222-228;230-236

Amidation sites:

Amino acids 207-211;254-258

Cell attachment sequence:

Amino acids 250-253

Page 184 of 359

WO 02/08288 PCT/US01/21066

71/246

WC0268268 [Be://E_W/06206286 opc.]

FIGURE 69

CCCACGCGTCCGAAACACTTTAAACCTGACCAGCTAAATGGATAAACCTAGCCTGCATAGCT TTTAAACTGGGGTCTCATACAGCACAGGAGGCCTACTTGCTTCAAGAACTGAAAATCCAGAG GATGAATTGCTTTATCTGGGAATGGCAAAAGCCAGCACAATAAGGAATGCCAGTTTGTATGG GGCTACTAGCTCACATGCGGGATCAGAATGGTGTGAATGACAGCCGCACTGTGTCATGAAGG TGGTGGTGGTTTCCGCACAAGAGACCAAATAAGAAGAAAGCTGAGAGAGGGGGGAAACGTTTTT GGATGACAAAGGATGGGTTTCCATTTAATTACGCAGCTGAAAGGCATGAGTGTGGTGCTGGT GCTACTTCCTACACTGCTGCTTGTTATGCTCACGGGTGCTCAGAGAGCTTGCCCAAAGAACT GCAGATGTGATGGCAAAATTGTGTACTGTGAGTCTCATGCTTTCGCAGATATCCCTGAGAAC ATTTCTGGAGGGTCACAAGGCTTATCATTAAGGTTCAACAGCATTCAGAAGCTCAAATCCAA TCAGTTTGCCGGCCTTAACCAGCTTATATGGCTTTATCTTGACCATAATTACATTAGCTCAGTG TACTTATCTGCACAATAAAACATTTCACCCAGTTCCCAATCTCCGCAATCTGGACCTCTCCT ACAATAAGCTTCAGACATTGCAATCTGAACAATTTAAAGGCCTTCGGAAACTCATCATTTTG CACTTGAGATCTAACTCACTAAAGACTGTGCCCATAAGAGTTTTTCAAGACTGTCGGAATCT TGATTTTTGGATTTGGGTTACAATCGTCTTCGAAGCTTGTCCCGAAATGCATTTGCTGGCC TCTTGAAGTTAAAGGAGCTCCACCTGGAGCACCAGTTTTCCAAGATCAACTTTGCTCAT TTTCCACGTCTCTACACCTCCGCTCAATTTACTTACAATGGAACAGGATTCGCTCCATTAG CCAAGGTTTGACATGGACTTGGAGTTCCTTACACAACTTGGATTTATCAGGGAATGACATCC AAGGAATTGAGCCGGGCACATTTAAATGCCTCCCCAATTTACAAAAATTGAATTTGGATTCC AACAAGCTCACCAATATCTCACAGGAAACTGTCAATGCGTGGATATCATTAATATCCATCAC ATTGTCTGGAAATATGTGGGAATGCAGTCGGAGCATTTGTCCTTTATTTTATTGGCTTAAGA ATTTCAAAGGAAATAAGGAAAGCACCATGATATGTGCGGGACCTAAGCACATCCAGGGTGAA AAGGTTAGTGATGCAGTGGAAACATATAATATCTGTTCTGAAGTCCAGGTGGTCAACACAGA AAGATCACCCTGGTGCCCCAAACTCCCCAGAAACCTCTGATTATCCCTAGACCTACCATCT TCAAACCTGACGTCACCCAATCCACCTTTGAAACACCAAGCCCTTCCCCAGGGTTTCAGATT CCTGGCGCAGAGCAAGAGTATGAGCATGTTTCATTTCACAAAATTATTGCCGGGAGTGTGGC TCTCTTTCTCTCAGTGGCCATGATCCTCTTGGTGATCTATGTGTCTTGGAAACGCTACCCAG CCAGCATGAAACAACTCCAGCAACACTCTCTTATGAAGAGGCGGCGGAAAAAGGCCAGAGAG TCTGAAAGACAAATGAATTCCCCTTTACAGGAGTATTATGTGGACTACAAGCCTACAAACTC TGAGACCATGGATATATCGGTTAATGGATCTGGGCCCTGCACATATACCATCTCTGGCTCCA GGGAATGTGAGATGCCACACCACATGAAGCCCTTGCCATATTACAGCTATGACCAGCCTGTG ATCGGGTACTGCCAGGCCCACCAGCCACTCCATGTCACCAAGGGCTATGAGACAGTGTCTCC AGAGCAGGACGAAAGCCCCGGCCTGGAGCTGGGCCGAGACCACAGCTTCATCGCCACCATCG CCAGGTCGGCAGCCGGCCATCTACCTAGAGAGAATTGCAAACTAACGCTGAAGCCAACTC CTCACTGGGGGGGGGGGGGGGGGGCCTTCATCTTAAAGGAGAATGGGTGTCCA CAATCGCGCAATCGAGCAAGCTCATCGTTCCTGTTAAAACATTTATGGCATAGGGAAAAAAA AAAAAAAAAAAAA

72/246

FIGURE 70

Page 185 of 359

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA142392

><subunit 1 of 1, 590 aa, 1 stop ><MW: 67217, pI: 9.26, NX(S/T): 4

MGFHLITOLKGMSVVLVLLPTLLLVMLTGAORACPKNCRCDGKIVYCESHAFADIPENIS GGSOGLSLRFNSIOKLKSNOFAGLNOLIWLYLDHNYISSVDEDAFOGIRRLKELILSSNK ITYLHNKTFHPVPNLRNLDLSYNKLOTLOSEOFKGLRKLIILHLRSNSLKTVPIRVFODC

RNLDFLDLGYNRLRSLSRNAFAGLLKLKELHLEHNOFSKINFAHFPRLFNLRSIYLOWNR IRSISOGLTWTWSSLHNLDLSGNDIOGIEPGTFKCLPNLOKLNLDSNKLTNISOETVNAW ISLISITLSGNMWECSRSICPLFYWLKNFKGNKESTMICAGPKHIOGEKVSDAVETYNIC . SEVOVVNTERSHLVPOTPOKPLIIPRPTIFKPDVTOSTFETPSPSPGFOIPGAEOEYEHV SFHKIIAGSVALFLSVAMILLVIYVSWKRYPASMKQLQQHSLMKRRRKKARESERQMNSP LQEYYVDYKPTNSETMDISVNGSGPCTYTISGSRECEMPHHMKPLPYYSYDOPVIGYCOA HQPLHVTKGYETVSPEQDESPGLELGRDHSFIATIARSAAPAIYLERIAN

Important features of the protein: Signal peptide:

Amino acids 1-30

WO0268268 [He://E-/W/00206286 opc]

Transmembrane domain: Amino acids 425-443

N-glycosylation sites:

Amino acids 58-62:126-130:291-295:501-505

Tyrosine kinase phosphorylation site:

Amino acids 136-143

N-myristoylation sites:

Amino acids 29-35;61-67;247-253;267-273;271-277;331-337;

502-508;512-518;562-568

Glycosyl hydrolases family:

Amino acids 310-319

Page 186 of 359

PCT/US01/21066

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288

73/246

FIGURE 71

WC-0098168 [file:///E-AV-09206238 opc.]

WO 02/08288 PCT/US01/21066

Page 187 of 359

74/246

FIGURE 72

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA143076

><subunit 1 of 1, 128 aa, 1 stop

><MW: 14332, pI: 4.83, NX(S/T): 0

MARILLLFPGUVAVCAVHGIFMDRLASKKLCADDECYYTISLASAQEDYNAPDCRFINV KKGQQIYYYSKLVKENGAGEFWAGSVYGDGQDEMGVVGYFPRNLVKEQRVYQEATKEVPT TDIDFFCE

Important features of the protein: Signal peptide:

Amino acids 1-14

N-myristoylation site: Amino acids 84-90

Page 138 of 359

WC0268268 [He://E-W/06206286 opc]

75/246

FIGURE 73

Page 189 of 559

76/246

FIGURE 74

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA143294 ><subunit 1 of 1, 175 aa, 1 stop, 1 unknown ><MW: 19888.97, pI: 9.08, NX(S/T): 0 MEKFSVSAILLLVAISGTLAKDTTVKSGSKKDPKDSRPKLPQTLSRGWGDQLIWTQTYEE ALYKSKTSNRPLMVIHHLDECPHSQALKKVFAENKEIQKLAEQFVLLNLIYETTDKHLSP DGQYVPRIVFVDPSLTVRADITGRYSNRLYAYEPSDTALLHDNMKKALKLLKTEL

Important features of the protein: Signal peptide: Amino acids 1-20

WCG208268 [Re://E/W/00206286 opc]

Page 190 of 359

WO0268268 [He://E-W/00206286 opc]

77/246

FIGURE 75

Page 191 of 359

78/246

FIGURE 76

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA143514

><subunit 1 of 1, 207 aa, 1 stop

><MW: 22896, pI: 8.93, NX(S/T): 0

MAALVEPLGLERDVSRAVELLERLQRSGELPPOKLQALQRVLQSRFCSAIREVYEQLYDT LDITGSAETRAHATAKATVAAFTASBCHAHPRVVELPKTDBGLGFNIMGGKEONSFIYIS RVIPGGVADRHGGLKRGDQLLSVNGVSVEGEQHEKAVELLKAAQGSVKLVVRYTPRVLEE MEARFEKWRSARRRQOHOSYSSLESRG

Tyrosine kinase phosphorylation site: Amino acids 51-59

WCG268268 [He://E-/WOG266286 opc]

N-myristoylation sites:

Amino acids 102-108;133-139

Cell attachment sequence:

Amino acids 136-139

PDZ domain (Also known as DHR or GLGF):

Amino acids 93-174

Page 192 of 359

PCT/US01/21066

WC0268268 [Be://E-W/00206286 epc]

WO 02/08288

79/246

FIGURE 77

CTGTCAGCTGAGGATCCAGCCGAAAGAGGAGCCAGGCACTCAGGCCACCTGAGTCTACTCAC CTGGACAACTGGAATCTGGCACCAATTCTAAACCACTCAGCTTCTCCGAGCTCACACCCCGG AGATCACCTGAGGACCCGAGCCATTGATGGACTCGGACGAGGACCGGGTTCGAGCACTCAGGA CTGTGGGTTTCTGTGCTGGCTGGTCTGCGGGAGCCTGCCAGGCACACCCCATCCCTGACTC CAGTCCTCTCCTGCAATTCGGGGGCCAAGTCCGGCAGCGGTACCTCTACACAGATGATGCCC AGCAGACAGAAGCCCACCTGGAGATCAGGGAGGATGGGACGGTGGGGGGGCGCTGCTGACCAG AGCCCGAAAGTCTCCTGCAGCTGAAAGCCTTGAAGCCGGGAGTTATTCAAATCTTGGGAGT CAAGACATCCAGGTTCCTGTGCCAGCGGCCAGATGGGGCCCTGTATGGATCGCTCCACTTTG ACCCTGAGGCCTGCAGCTTCCGGGAGCTGCTTCTTGAGGACGGATACAATGTTTACCAGTCC GAAGCCCACGGCCTCCCGCTGCACCTGCCAGGGAACAAGTCCCCACACCGGGACCCTGCACC CCGAGGACCAGCTCCCTGCCACTACCAGGCCTGCCCCCGCACTCCCGGAGCCACCCG GAATCCTGGCCCCCAGCCCCCGATGTGGGCTCCTCGGACCCTCTGAGCATGGTGGGACCT ${\tt TCCCAGGGCCGAAGCCCCAGCTACGCTTCC} {\tt TGA} {\tt AGCCAGAGGCTGTTTACTATGACATCTCC}$ AAAAAAG

WC-0204058 [He-I/IE AV 00205235 opc.]

PCT/US01/21066

Page 193 of 359

80/246

FIGURE 78

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA144841

><subunit 1 of 1, 208 aa, 1 stop

><MW: 22187, pI: 5.08, NX(S/T): 1

MDSDETGFEHSGLWVSVLAGLLGACQAHPIPDSSPLLQFGGQVRQRYLYTDDAQQTEAHL EIREDGTVGGAADOSPESLLQLKALKPGVIQILGVKTSRFLCQRPDGALYGSLHFDPEAC SFRELLLEDGYNVYQSEAHGLPLHLPGNKSPHRDPAPRGPARFLPLPGLPPALPEPPGIL APOPPDVGSSDPLSMVGFSQGRSPSYAS

Important features of the protein:

Signal peptide:

WO 02/08288

Amino acids 1-27

N-myristoylation sites:

Amino acids 12-18;20-26;23-29;66-72;94-100;107-113;168-174

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 15-26

HBGF/FGF family proteins:

Amino acids 57-73:80-131

Page 194 of 359

81/246

WC0268268 [Be://E_W/06206286 opc.]

FIGURE 79

CCAGCAGGGAACCAGACCTCCCCGGGGCCACAGAGGACTACTCCTATGGCAGCTGGTAC ATCGATGAGCCCCAGGGGGGCGAGGAGCTCCAGCCAGAGGGGGAAGTGCCCTCCTGCCAC ACCAGCATACCACCGGCCTGTACCACGCCTGCCTGGCCTCGCTGTCAATCCTTGTGCTG CTGCTCCTGGCCATGCTGGTGAGGCGCCGCCAGCTCTGGCCTGACTGTGTGCGTGGCAGG CCCGGCCTGCCCAGCCCTGTGGATTTCTTGGCTGGGGACAGGCCCCGGGCAGTGCCTGCT GCTGTTTTCATGGTCCTCCTGAGCTCCCTGTGTTTTGCTGCTCCCCGACGAGGACGCATTG CCCTTCCTGACTCTCGCCTCAGCACCCAGCCAAGATGGGAAAACTGAGGCTCCAAGAGGG GCCTGGAAGATACTGGGACTGTTCTATTATGCTGCCCTCTACTACCCTCTGGCTGCCTGT GCCACGGCTGGCCACACAGCTGCACACCTGCTCGGCACACGCTGTCCTGGGCCCACCTT GGGGTCCAGGTCTGGCAGAGGGCAGAGTGTCCCCAGGTGCCCAAGATCTACAAGTACTAC TCCCTGCTGGCCTCCCTGCTCTGGGCCTCGGATTCCTGAGCCTTTGGTACCCT GTGCAGCTGGTGAGAAGCTTCAGCCGTAGGACAGGAGCAGGCTCCAAGGGGCTGCAGAGC AGCTACTCTGAGGAATATCTGAGGAACCTCCTTTGCAGGAAGAAGCTGGGAAGCAGCTAC CACACCTCCAAGCATGGCTTCCTGTCCTGGGCCCGCGTCTGCTTGAGACACTGCATCTAC ACTCCACAGCCAGGATTCCATCTCCCGCTGAAGCTGGTGCTTTCAGCTACACTGACAGGG ACGCCATTTACCAGGTGGCCCTGCTGCTGCTGGTGGGCGTGGTACCCACTATCCAGAAG GTGAGGGCAGGGTCACCACGGATGTCTCCTACCTGCTGGCCGGCTTTGGAATCGTGCTC TCCGAGGACAAGCAGGAGGTGGAGCTGGTGAAGCACCATCTGTGGGCTCTGGAAGTG TGCTACATCTCAGCCTTGGTCTTGTCCTGCTTACTCACCTTCCTGGTCCTGATGCGCTCA CTGGTGACACACAGGACCAACCTTCGAGCTCTGCACCGAGGAGCTGCCCTGGACTTGAGT CCCTTGCATCGGAGTCCCCATCCCTCCCGCCAAGCCATATTCTGTTGGATGAGCTTCAGT GCCTACCAGACAGCCTTTATCTGCCTTGGGCTCCTGGTGCAGCAGATCATCTTCTTCCTG GGAACCACGGCCCTGGCCTTCCTGGTGCTCATGCCTGTGCTCCATGGCAGGAACCTCCTG CTCTTCCGTTCCCTGGAGTCCTCGTGGCCCTTCTGGCTGACTTTGGCCCTGGCTGTGATC CTGCAGAACATGGCAGCCCATTGGGTCTTCCTGGAGACTCATGATGGACACCCACAGCTG GGTGCCATGGTGGCCACCTGGCGAGTGCTCCTCTCTGCCCTCTACAACGCCATCCACCTT GGCCAGATGGACCTCAGCCTGCCACCGAGAGCCGCCACTCTCGACCCCGGCTACTAC ACGTACCGAAACTTCTTGAAGATTGAAGTCAGCCAGTCGCATCCAGCCATGACAGCCTTC TGCTCCTGCTCCTGCAAGCGCAGAGCCTCCTACCCAGGACCATGGCAGCCCCCCAGGAC AGCCTCAGACCAGGGGAGGAAGACGAAGGGATGCAGCTGCTACAGACAAAGGACTCCATG GCCAAGGGAGCTAGGCCCGGGGCCAGCCGCGGGGGTCGCTGGGGTCTGGCCTACACG CTGCTGCACACCCAACCCTGCAGGTCTTCCGCAAGACGGCCCTGTTGGGTGCCAATGGT GCCCAGCCCTGAGGGCAGGGAAGGTCAACCCACCTGCCCATCTGTGCTGAGGCATGTTCC TGCCTACCATCCTCCCTCCCGGCTCTCCTCCCAGCATCACACCAGCCATGCAGCCA GGCTCTGCTCCACCCACTTGGCTATGGGAGAGCCAGCAGGGGTTCTGGAGAAAAAACTG GTGGGTTAGGGCCTTGGTCCAGGAGCCAGTTGAGCCAGGGCAGCCACATCCAGGCGTCTC CCTACCCTGGCTCTGCCATCAGCCTTGAAGGGCCTCGATGAAGCCTTCTCTGGAACCACT CACCCCTCAGCGCCACGGACCTCTCTGGGGAGTGGCCGGAAAGCTCCCGGTCCTCTGGC CTGCAGGGCAGCCCAAGTCATGACTCAGACCAGGTCCCACACTGAGCTGCCCACACTCGA GAGCCAGATATTTTGTAGTTTTTATGCCTTTGGCTATTATGAAAGAGGTTAGTGTTTC

Page 195 of 359

PCT/US01/21066

82/246

FIGURE 80

Protein File:

WO 02/08288

WO0268268 [He://E-/W/00206286 opc]

MW: 73502.97, pI: 9.26

MSSOPAGMOTSPGATEDYSYGSWYIDEPQGGEELOPEGEVSSCHTSIPPGLYHACLASLS
ILVLLLLAMLYRROLWPDCVORGREGLSPVDFLAGDRPRAVPAAVFWVLLSSLCLLPD
EDALPFLTLASAPSODGKTEAPPGAWKILGLFYYAALYYLAACATAGHTAAHLLGSTLS
WAHLGYOVWORAECPOVPKIYKYYSLLASLPLLLGLGFLSLWYPVOLVRSFSRRTGAGSK
GLGSSYSESYLKINLLCKKKLGSSYHRSKHGFLSWARVCLRHCLYTPQPGFHLPLKIVLSA
TLTGTAIYQVALLLLVGVUPTIGKVRAGVTTDVSYLLAGFGIVLSBDKGBVVELVKHHLW
ALEVCYISALVLSCLLFLUMRSLUFHTRNLRAHRGAADLLSPHRSPHSSGNAFCW
MSFSAYOTAFICLGLLVOOIIFFLGTTALAFLVLMPVLHGRAHLLFRSLESSWPFWLTLA
LAVILONMAAHWVELETHDGHPQTTRRVLYAATFLLEPLMVLVGAMVATWRVLLSALYN
AFNOBSLPFGATTLUFGYTYTNFLKIEVSGSPFMATAFCSLLLQAGSLLDFRMA
APODSLRPGEEDEGMOLLOTKDSMAKGARPGASRGRARWGLAYTLLHNPTLOVFRKTALL
GANGAOP

Important features of the protein:

Transmembrane domains: Amino acids 54-69:1

54-69;102-119;148-166;207-222;301-320;

364-380;431-451;474-489;512-531

N-glycosylation site:

Amino acids 8-12

N-myristoylation sites:

Amino acids 50-56;176-182;241-247;317-323;341-347;525-531;

627-633;631-637;640-646;661-667

Prokaryotic membrane lipoprotein lipid attachment site: Amino acids 364-375

ATP/GTP-binding site motif A (P-loop):

Amino acids 132-140

Page 196 of 359

83/246

WC0268268 [like://E_W/06206286 opc.]

FIGURE 81

AAAAAATACAGCAGGTGAAGGAGGTTGGAGAGTAGGGGGTGGAGGGCCCACGCAGCACTTGT CCTTCACCCTGGAGGGGATCTGTTACATGCCCCAGATTGCTGGTCCCCTAGAAATGTTACTG AGGCAGCCTCTGCATTTTTGCAGGGATTGTTTTCTACTGTTTGACATTCACGTAACCTCCTA ACGCTGTCTGGGGAAGATGCTACCCCCTGCTCTCCCCGTCTTTCCTGCACTCTCAGCAATGG GATGGGCTGACTGATGCCCTGTGGGCTGGAAAGCTGACCACAGTTGCTGCAGACCAGACCCC CTCACATAGTGAGTGCTGGGCTGAGGAATCCAGGAGAGCCCGAGGGGGGACACTGAAGGTGT TATTTGCTAAGAATGCCAATCCTGACGCTCAGCCTTCAACTCATCTTGTTATTAATACCATC AATATCCCATGAGGCTCATAAAACGAGTCTTTCTTCTTGGAAACATGACCAAGATTGGGCAA ACGTCTCCAACATGACTTTCAGCAACGGAAAACTAAGAGTCAAAGGCATTTATTACCGGAAT GCCGACATTTGCTCTCGACATCGCGTAACCTCAGCAGGCCTAACTCTGCAGGACCTTCAGCT ATGGTGTAATTTGAGGTCAGTGGCCAGAGGACAGATCCCGTCTACATTATGAGTGAAGCGGAGA GCTACTGCAGGGTTCTGAGCAGAGTCCTAATTTATATTTTAGAAGAATCATCATGGCTCCTA GATTAGGAATAAAACGAAGGGGCCCAGGGATGGAAACGATGAGTCCAGTTGGGTTACTGCAA AGATCCAGGCCAGAAATCCAGGCACAGTGGCACACACCTGAGTCCCAGATAATTCCACCTAC TGGTCCTGCTCTGTGGCCTACTGGTCCGAGTCCAGCCCCGACTGATTTCTGGGCCTGTAATG TCTAAAAACGCTCCCTGCTGATGTTTTGCAAGTGACTGTGTTACTTGAAGGCAGTTCCTAGG ATAAACTAGTCGCTTTATCATTACAGAATCATTCACTGAGCATCAACTATGTAACCAGCATT GGGTTGGGTGCCAGAGATCCAAAGCTAAGACACCAAAACCTGCTCTCCAGGAAACGAGAGGC TGAGAA

84/246

FIGURE 82

Page 197 of 359

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA149995
><subunit 1 of 1, 95 aa, 1 stop
><mW: 10704, pI: 10.00, NX(S/T): 2
MAILTLSLQLILLLIPSISHEAHKTSLSSWKHDQDWANVSNMTFSNGKLRVKGIYYRNAD
ICSRHRYTSAGLTLODLOLDWCNLRSVARGOIPSTL</pre>

Important features of the protein: Signal peptide:

Amino acids 1-19

WCG208268 [Re://E/W/00206286 opc]

N-glycosylation sites: Amino acids 38-42;41-45

N-myristoylation site:

Amino acids 89-95

WC6268368 (Her//E/W/06266286 opc)

WO 02/08288 PCT/US01/21066

Page 198 of 359

85/246

FIGURE 83

AATAGAAGTCCTCAGGACGGAGCAGAGGTGGCCGGCGGGCCGGCTGACTGCGCTCTGCTT TCTTTCCATAACCTTTTCTTTCGGACTCGAATCACGGCTGCTGCGAAGGGTCTAGTTCCGGA $\tt CACTAGGGTGCCCGAACGCGCTGATGCCCCGAGTGCTCGCAGGGCTTCCCGCTAACC\underline{\textbf{ATG}}CT$ GCCGCCGCGGCCCGCAGCTGCCTTGGCGCTGCTGTGCTCCTGCTACTGCTGGTGGTGC TGACGCCCCCCGACCGGCGCAAGGCCATCCCCAGGCCCAGATTACCTGCGGCGCGGCTGG ATGCGCTGCTAGCGGAGGGCGAGGGCTGCGCTCCCTGCCGGCCAGAAGAGTGCGCCGCCC GCGGGCTGCCTGGCGGCAGGGTGCGCGACGCGTGCGGCTGCTGCTGGGAATGCGCCAACC TCGAGGGCCAGCTCTGCGACCTGGACCCCAGTGCTCACTTCTACGGGCACTGCGGCGAGCAG CTTGAGTGCCGGCTGGACACAGGCGGCGACCTGAGCCGCGGAGAGGTGCCGGAACCTCTGTG TGCCTGTCGTTCGCAGAGTCCGCTCTGCGGGTCCGACGGTCACACCTACTCCCAGATCTGCC GCCTGCAGGAGGCGGCCCGCTCGGCCCGATGCCAACCTCACTGTGGCACACCCGGGGCCC TGCGAATCGGGGCCCCAGATCGTGTCACATCCATATGACACTTGGAATGTGACAGGGCAGGA GCTTGGACATCCAGCTGCCAGGGGATGACCCCCACATCTCTGTGCAGTTTAGGGGTGGACCC CAGAGGTTTGAGGTGACTGGCTGCCAGATCCAGGCTGTGCGTCCCAGTGATGAGGGCAC TTACCGCTGCCTTGGCCGCAATGCCCTGGGTCAAGTGGAGGCCCCTGCTAGCTTGACAGTGC TCACACCTGACCAGCTGAACTCTACAGGCATCCCCCAGCTGCGATCACTAAACCTGGTTCCT GAGGAGGAGGCTGAGAGTGAAGAGAATGACGATTACTACTACGTCCAGAGCTCTGGCCCATG GGGGTGGGTGAGCGGCTATAGTGTTCATCCCTGCTCTTGAAAAGACCTGGAAAGGGGAGCAG GGTCCCTTCATCGACTGCTTTCATGCTGTCAGTAGGGATGATCATGGGAGGCCTATTTGACT CCAAGGTAGCAGTGTGGTAGGATAGAGACAAAAGCTGGAGGAGGGTAGGGAGAGAAGCTGAG ACCAGGACCGGTGGGGTACAAAGGGGCCCATGCAGGAGATGCCCTGGCCAGTAGGACCTCCA ACAGGTTGTTTCCCAGGCTGGGGTGGGGGCCTGAGCAGACACAGAGGTGCAGGCACCAGGAT TCTCCACTTCTTCCAGCCCTGCTGGGCCACAGTTCTAACTGCCCTTCCTCCCAGGCCCTGGT TCTTGCTATTTCCTGGTCCCCAACGTTTATCTAGCTTGTTTGCCCTTTCCCCAAACTCATCT TCCAGAACTTTTCCCTCTCTCTAAGCCCCAGTTGCACCTACTAACTGCAGTCCCTTTTGCT GTCTGCCGTCTTTTGTACAAGAGAGAGAACAGCGGAGCATGACTTAGTTCAGTGCAGAGAGA TTT

Page 199 of 359

86/246

FIGURE 84

>>/usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA167678
><subunit 1 of 1, 304 aa, 1 stop
><mw: 32945, pi: 4.69, NX(s/T): 3
MIPPPRPAAALALPVILLILUVUTPPPTGARPSPGPDYLRRGWMRLLAEGEGCAPCRPEE
CAAPRGCLAEGRVRDAGCGCWECANLEGQLCDLDPSAHFYGHCGEQLECRLDTGGDLSRGE
VPEPLCACRSQSPLCGSDGHTYSQICRLQEAARARPDANLTVAHPGPCESGPQIVSHPYD
TMNVTGQDVIFGCEVFRYPMASIEWRKDGLDIQLFGDDPHISVQFRGGPQRFEVTGWLQI
OAVRPSDEGTYRCLGFMALGGVEAPASLTVLTPDOLDISTGIPOLRSINLIVPEEEABSEEN

Important features of the protein:

Signal peptide:

DDYY

WC0268268 (Mer//E_W/06Z06286 opc.)

Amino acids 1-30

N-glycosylation sites:

Amino acids 159-163;183-187;277-281

Tyrosine kinase phosphorylation site:

Amino acids 244-252

N-myristoylation sites:

Amino acids 52-58;66-72;113-119;249-255

Kazal-type serine protease inhibitor domain:

Amino acids 121-168

Immunoglobulin domain:

Amino acids 186-255

Insulin-like growth factor binding proteins:

Amino acids 53-90

87/246

FIGURE 85

CAAAGCGGCGGTGTCCGCGGTGCCGGCTGGGGGCGAGAGGCGGCGGTGGGCTCCCTGGGG TGTGTGAGCCCGGTGATGGAGCCGGGCCCGACAGCCGCGCAGCGGAGGTGTTCGTTGCCGCC GTGGCTGCCGCTGGGGCTGCTGTGTGTCGGGGCTGGCCCTGGGCGCGCTCCCCTTCGGCA GCAGTCCGCACAGGGTCTTCCACGACCTCCTGTCGGAGCAGCAGTTGCTGGAGGTGGAGGAC TTGTCCCTGTCCCTGCAGGGTGGAGGCTGGGGCCTCTGTCGCTGCCCCGGACCTGCC GGATCTGGATCCTGAGTGCCGGGAGCTCCTGCTGGACTTCGCCAACAGCAGCGCAGAGCTGA CAGGGTGTCTGGTGCGCAGCGCCCGGCCCGTGCGCCTCTGTCAGACCTGCTACCCCCTCTTC CAACAGGTCGTCAGCAAGATGGACAACATCAGCCGAGCCGCGGGGAATACTTCAGAGAGTCAG AGTTGTGCCAGAAGTCTCTTAATGGCAGATAGAATGCAAATAGTTGTGATTCTCTCAGAATT TATCAAACAGCACAGTATATTTCCTTAATCTATTTAATCACACCCTGACCTGCTTTGAACAT AACCTTCAGGGGAATGCACATAGTCTTTTACAGACAAAAATTATTCAGAAGTATGCAAAAA TTGAGAATAAGGCTGAACCTGGAACACATTTATGCATTGATGTGGAAGATGCAATGAACATC ACTCGAAAACTATGGAGTCGAACTTTCAACTGTTCAGTCCCTTGCAGTGACACAGTGCCTGT AATTGCTGTTTCTGTTCTCTTTCTACCTGTTGTCTTCTACCTTAGTAGCTTTCTTC ACTCAGAGCAAAAGAAACGCAAACTCATTCTGCCCAAACGTCTCAAGTCCAGTACCAGTTTT GCAAATATTCAGGAAAATTCAAAC<u>TGA</u>GACCTACAAAATGGAGAATTGACATATCACGTGAA TGAATGGTGGAAGACAACTTGGTTTCAGAAAGAAGATAAACTGTGATTTGACAAGTCAAG TTTTCCACTTCTTTCTAACAGATTTGGATATTTTTAATTTCCAG

Page 201 of 359

WO 02/08288 PCT/US01/21066

88/246

FIGURE 86

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA168028

><subunit 1 of 1, 334 aa, 1 stop

><MW: 37257, pI: 5.95, NX(S/T): 10

MEPGPTAAQRRCSLPPWLPLGLLLWSGLALGALPFGSSPHRVFHDLLSEQQLLEVEDLSL SLLQGGGLGPLSLPPDLPDLDPECRELLLDFANSSAELTGCLVRSARPVRLCQTCYPLFQ QVVSKMDNISRAAGNTSESOSCARSLLMADRMOIVVILSEFFNTTWOEANCANCLTNNSE ELSNSTVYFLNLFNHTLTCFEHNLOGNAHSLLOTKNYSEVCKNCREAYKTLSSLYSEMOK MNELENKAEPGTHLCIDVEDAMNITRKLWSRTFNCSVPCSDTVPVIAVSVFILFLPVVFY LSSFLHSEQKKRKLILPKRLKSSTSFANIOENSN

Important features of the protein:

Signal peptide:

WC0268268 (Mer//E_W/06Z06286 opc.)

Amino acids

Transmembrane domain:

Amino acids 278-300

N-glycosylation sites:

Amino acids

93-97;128-132;135-139;163-167;177-181; 184-188;194-198;216-220;263-267;274-278

cAMP- and cGMP-dependent protein kinase phosphorylation site:

Amino acids 10-14

N-myristoylation sites:

27-33;206-212;251-257 Amino acids

Leucine zipper pattern:

Amino acids 190-212

Page 202 of 359

89/246

WC0268268 [like]//E_W/06206286 opc.]

FIGURE 87

ATGCTGGTAGCCGGCTTCCTGCTGGCGCTGCCGCCGAGCTGGGCCGCGGGCGCCCCCAGGGC GGGCAGGCGCCCGCGGCGGGGGCTGCGCGGACCGGCCGGAGGAGCTACTGGAGCAGC TGTACGGGCGCCTGGCGGCGTGCTCAGTGCCTTCCACCACACGCTGCAGCTGGGGCCG CGTGAGCAGCCGCGAACGCGAGCTGCCCGGCAGGGGGCAGGCCCGCGACCGCCGCTTCCG GCCGCCCACCAACCTGCGCAGCGTGTCGCCCTGGGCCTACAGAATCTCCTACGACCCGGCGA GGTACCCCAGGTACCTGCCTGAAGCCTACTGCCTGTGCCGGGGCTGCCTGACCGGGCTGTTC GGCGAGGAGGACGTGCGCTTCCGCAGCGCCCCTGTCTACATGCCCACCGTCGTCCTGCGCCG CACCCCGCCTGCGCCGGCCGTTCCGTCTACACCGAGGCCTACGTCACCATCCCCGTGG GCTGCACCTGCGTCCCCGAGCCGGAGAAGGACGCAGCATCAACTCCAGCATCGACAAA CAGGGCGCCAAGCTCCTGCTGGGCCCCAACGACGCCCCGCTGGCCCCTCAGGCCGGTCCTG CCCCGGGAGGTCTCCCCGGCCCGCATCCCGAGGCGCCCAAGCTGGAGCCGCCTGGAGGGCTC GGTCGGCGACCTCTGAAGAGAGTGCACCGAGCAAACCAAGTGCCGGAGCACCAGCGCCGCCT AAGCAAGCGTGGCTGGAAGCTGATGGGAAACGACCCGGCACGGCATCCTGTGTGCGGC CCGCATGGAGGGTTTGGAAAAGTTCACGGAGGCTCCCTGAGAGCCTCTCAGATCGGCTGCT GCGGGTGCAGGGCGTGACTCACCGCTGGGTGCTTGCCAAAGAGATAGGGACGCATATGCTTT TTAAAGCAATCTAAAAATAATAATAAGTATAGCGACTATATACCTACTTTTAAAATCAACTG TTTTGAATAGAGGCAGAGCTATTTTATATTATCAAATGAGAGCTACTCTGTTACATTTCTTA ACATATAAACATCGTTTTTTACTTCTTCTGGTAGAATTTTTTAAAGCATAATTGGAATCCTT GGATAAATTTTGTAGCTGGTACACTCTGGCCTGGGTCTCTGAATTCAGCCTGTCACCGATGG GGCCTCCAGGTGGACCAAAGGGATGCACAGGCGGCTCGCATGCCCCAGGGCCAGCTAAGAGT TCCAAAGATCTCAGATTTGGTTTTAGTCATGAATACATAAACAGTCTCAAACTCGCACAATT TTTTCCCCCTTTTGAAAGCCACTGGGGCCAATTTGTGGTTAAGAGGTGGTGAGATAAGAAGT GGAACGTGACATCTTTGCCAGTTGTCAGAAGAATCCAAGCAGGTATTGGCTTAGTTGTAAGG GCTTTAGGATCAGGCTGAATATGAGGACAAAGTGGGCCACGTTAGCATCTGCAGAGATCAAT GAAAGTCTGTCTCTGAACACAATTATTTGTAAAAGTTAGTAGTTCTTTTTTAAATCATTAAA AGAGGCTTGCTGAAGGAT

#C0008088 [##/#F/W05008289 opt] Page 203 od 35%

WO 02/08288 PCT/US01/21066

90/246

FIGURE 88

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA173894
><subunit 1 of 1, 202 aa, 1 stop</pre>

><subunit 1 of 1, 202 aa, 1 stop ><MW: 21879, pI: 9.30, NX(S/T): 2

MLVAGFILALPPSWAAGAPRAGRRPARPRGCADRPEELLEQLYGRLAAGVLSAFHHTLQL GFREQARNASCPAGGRPGDRRFRPPTNLRSVSPWAYRTSYDPARYPRYLPEAYCLCRGCL TGLFGEEDVRFRSAPYYMPTVVLRRTPACAGGRSVYTEAYVTIPVGCTCVPEPEKDADSI NSSIDKQGAKLLLGPNDAPAGP

Important features of the protein: Signal peptide:

Amino acids 1-15

N-qlycosylation sites:

Amino acids 68-72;181-185

Tyrosine kinase phosphorylation site:

Amino acids 97-106

N-myristoylation sites:

Amino acids 17-23;49-55;74-80;118-124

Amidation site:

Amino acids 21-25

Page 204 of 359

WO 02/08288 PCT/US01/21066

91/246

WC6268368 [Her//E/W/06266286 opc]

FIGURE 89

CCGGGGCCTCCGGAGAACGCTGTCCCATGAACGTGCGGGGAGCGGCCCCCGGCGTCCGCGCG TCCCCGCGTCCCTGGCAATTCCCGACTTCCCAACGCCTTCCCGCTGGCAGCCCCGAAGCCGC ACCATGTTCCGCCTCTGGTTGCTGCCGGCCCGGGCCTCCTGGCGTCAAGACCCGGT TTCAGAAATAGAATATGAACAAATATCCTATATTATTCCAATAGATGAGAAACTGTACACTG TGCACCTTAAACAAAGATATTTTTTAGCAGATAATTTTATGATCTATTTGTACAATCAAGGA TCTATGAATACTTATTCTTCAGATATTCAGACTCAATGCTACTATCAAGGAAATATTGAAGG ATATCCAGATTCCATGGTCACACTCAGCACGTGCTCTGGACTAAGAGGAATACTGCAATTTG AAAATGTTTCTTATGGAATTGAGCCTCTGGAATCTGCAGTTGAATTTCAGCATGTTCTTTAC AAATTAAAGAATGAAGACAATGATATTGCAATTTTTATTGACAGAAGCCTGAAAGAACAACC TTTATCTAGAAATGCATATTGTGGTGGACAAAACTTTGTATGATTACTGGGGCTCTGATAGC ATGATAGTAACAAATAAAGTCATCGAAATTGTTGGCCTTGCAAATTCAATGTTCACCCAATT TAAAGTTACTATTGTGCTGTCATCATTGGAGTTATGGTCAGATGAAAATAAGATTTCTACAG TTGGTGAGGCAGATGAATTATTGCAAAAATTTTTAGAATGGAAACAATCTTATCTTAACCTA AGGCCTCATGATATTGCATATCTACTAATTTATATGGATTATCCTCGTTATTTGGGAGCAGT GTTTCCTGGAACAATGTGTATTACTCGTTATTCTGCAGGAGTTGCATTGTACCCCAAGGAGA TAACTCTGGAGGCATTTGCAGTTATTGTCACCCAGATGCTGGCACTCAGTCTGGGAATATCA TATGACGACCCAAAGAAATGTCAATGTTCAGAATCCACCTGTATAATGAATCCAGAAGTTGT GCAATCCAATGGTGTGAAGACTTTTAGCAGTTGCAGTTTGAGGAGCTTTCAAAATTTCATTT GTCTGTGGCAATGGCAGATTGGAGGGAAATGAAATCTGTGATTGTGGTACTGAGGCTCAATG TGGACCTGCAAGCTGTTGTGATTTTCGAACTTGTGTACTGAAAGACGGAGCAAAATGTTATA AAGGACTGTGCTGCAAAGACTGTCAAATTTTACAATCAGGCGTTGAATGTAGGCCGAAAGCA CATCCTGAATGTGACATCGCTGAAAATTGTAATGGAAGCTCACCAGAATGTGGTCCTGACAT AACTTTAATCAATGGACTTTCATGCAAAAATAATAAGTTTATTTGTTATGACGGAGACTGCC ATGATCTCGATGCACGTTGTGAGAGTGTATTTGGAAAAGGTTCAAGAAATGCTCCATTTGCC TGCTATGAAGAAATACAATCTCAATCAGACAGATTTGGGAACTGTGGTAGGGATAGAAATAA CTCGAAAGCCTTTCCATCAAGAAAATGGTGATGTGATTTATGCTTTCGTACGAGATTCTGTA TGCATAACTGTAGACTACAAATTGCCTCGAACAGTTCCAGATCCACTGGCTGTCAAAAATGG CTCTCAGTGTGATATTGGGAGGGTTTGTGTAAATCGTGAATGTGTAGAATCAAGGATAATTAAG GCTTCAGCACATGTTTGTTCACAACAGTGTTCTGGACATGGAGTGTGATTCCAGAAACAA GTGCCATTGTTCGCCAGGCTATAAGCCTCCAAACTGCCAAATACGTTCCAAAGGATTTTCCA TATTTCCTGAGGAAGATATGGGTTCAATCATGGAAAGACATCTGGGAAGACTGAAAACACC TGGCTTCTAGGTTTCCTCATTGCTCTTCCTATTCTCATTGTAACAACCGCAATAGTTTTGGC AAGGAAACAGTTGAAAAAGTGGTTCGCCAAGGAAGGAATTCCCAAGTAGCGAATCTAAAT CGGAAGGTAGCACACAGACATATGCCAGCCAATCCAGCTCAGAAGGCAGCACTCAGACATAT GCCAGCCAAACCAGATCAGAAAGCAGCAGTCAAGCTGATACTAGCAAATCCAAATCAGAAGA TAGTGCTGAAGCATATACTAGCAGATCCAAATCACAGGACAGTACCCAAACACAAAGCAGTA GTAACTAGTGATTCCTTCAGAAGGCAACGGATAACATCGAGAGTCTCGCTAAGAAATGAAAA TTCTGTCTTTCCTTCCGTGGTCACAGCTGAAAGAACAATAAATTGAGTGTGGATC

WO0268268 [He://E-W/00206286 opc] Page 205 of 359

> WO 02/08288 PCT/US01/21066

92/246

FIGURE 90

```
></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA176775
```

><subunit 1 of 1, 787 aa, 1 stop

><MW: 87934, pI: 5.49, NX(S/T): 4

MFRLWLLLAGLCGLLASRPGFONSLLOIVIPEKIOTNTNDSSEIEYEOISYIIPIDEKLY TVHLKORYFLADNFMIYLYNOGSMNTYSSDIOTOCYYOGNIEGYPDSMVTLSTCSGLRGI LOFENVSYGIEPLESAVEFOHVLYKLKNEDNDIAIFIDRSLKEOPMDDNIFISEKSEPAV PDLFPLYLEMHIVVDKTLYDYWGSDSMIVTNKVIEIVGLANSMFTOFKVTIVLSSLELWS DENKISTVGEADELLOKFLEWKOSYLNLRPHDIAYLLIYMDYPRYLGAVFPGTMCITRYS AGVALYPKEITLEAFAVIVTOMLALSLGISYDDPKKCOCSESTCIMNPEVVOSNGVKTFS SCSLRSFONFISNVGVKCLONKPOMOKKSPKPVCGNGRLEGNEICDCGTEAOCGPASCCD FRTCVLKDGAKCYKGLCCKDCOILOSGVECRPKAHPECDIAENCNGSSPECGPDITLING LSCKNNKFICYDGDCHDLDARCESVFGKGSRNAPFACYEEIQSQSDRFGNCGRDRNNKYV FCGWRNLICGRLVCTYPTRKPFHQENGDVIYAFVRDSVCITVDYKLPRTVPDPLAVKNGS QCDIGRVCVNRECVESRIIKASAHVCSQQCSGHGVCDSRNKCHCSPGYKPPNCQIRSKGF SIFPEEDMGSIMERASGKTENTWLLGFLIALPILIVTTAIVLARKQLKKWFAKEEEFPSS ESKSEGSTQTYASQSSSEGSTQTYASQTRSESSSQADTSKSKSEDSAEAYTSRSKSQDST OTOSSSN

Important features of the protein:

Signal peptide:

Amino acids 1-16

Transmembrane domain:

309-326;681-705 Amino acids

N-glycosylation sites:

Amino acids 39-43;125-129;465-469;598-602

Glycosaminoglycan attachment site:

Amino acids 631-635

Tyrosine kinase phosphorylation site:

Amino acids 269-276

N-myristoylation sites:

Amino acids 13-19;82-88;99-105;218-224;401-407;634-640;

726-732;739-745

EGF-like domain proteins:

Amino acids 642-654

Disintegrins proteins:

Amino acids 400-407; 422-472; 403-453; 467-517; 634-684

Reprolysin (M12B) family zinc metalloprotease:

Amino acids 186-383

Reprolysin family propeptide:

Amino acids 63-176

Page 206 of 359

WC0268268 [Be://E_W/06206286 opc.]

WO 02/08288 PCT/US01/21066

93/246

FIGURE 91

CACCAGACAGCACTCCAGCACTCTGTTTGGGGGGCATTCGAAACCAGCAAAATCACTCATAAA AGGCAAAAATTGCAAAAAAAAATAGTAATAACCAGCATGGCACTAAATAGACCATGAAAAG ACATGTGTGTGCAGTATGAAAATTGAGACAGGAAGGCAGAGTGTCAGCTTGTTCCACCTCAG CTGGGAATGTGCATCAGGCAACTCAAGTTTTTCACCACGGCATGTGTCTGTGAATGTCCGCA AAACATTCTCTCCCCAGCCTTCATGTGTTAACCTGGGGATGATGTGGACCTGGGCACTGTGG ATGCTCCCTTCACTCTGCAAATTCAGCCTGGCAGCTCTGCCAGCTAAGCCTGAGAACATTTC CTGTGTCTACTACTATAGGAAAAATTTAACCTGCACTTGGAGTCCAGGAAAGGAAACCAGTT ATACCCAGTACACAGTTAAGAGAACTTACGCTTTTGGAGAAAAACATGATAATTGTACAACC AGATAATTATACCATTGAGGTGGAAGCTGAAAATGGAGATGGTGTAATTAAATCTCATATGA CATACTGGAGATTAGAGAACATAGCGAAAACTGAACCACCTAAGATTTTCCGTGTGAAACCA GTTTTGGGCATCAAACGAATGATTCAAATTGAATGGATAAAGCCTGAGTTGGCGCCTGTTTC ACTTCGCTAAGAACCGTAAGGATAAAAACCAAACGTACAACCTCACGGGGCTGCAGCCTTTT ACAGAATATGTCATAGCTCTGCGATGTGCGGTCAAGGAGTCAAAGTTCTGGAGTGACTGGAG CCAAGAAAAATGGGAATGACTGAGGAAGAAGCTCCATGTGGCCTGGAACTGTGGAGAGTCC TGAAACCAGCTGAGGCGGATGGAAGAAGGCCAGTGCGGTTGTTATGGAAGAAGGCAAGAGGA GCCCCAGTCCTAGAGAAAACACTTGGCTACAACATATGGTACTATCCAGAAAGCAACACTAA CCTCACAGAAACAATGAACACTACTAACCAGCAGCTTGAACTGCATCTGGGAGGCGAGAGCT TTTGGGTGTCTATGATTTCTTATAATTCTCTTGGGAAGTCTCCAGTGGCCACCCTGAGGATT CCAGCTATTCAAGAAAAATCATTTCAGTGCATTGAGGTCATGCAGGCCTGCGTTGCTGAGGA CCAGCTAGTGGTGAAGTGGCAAAGCTCTGCTCTAGACGTGAACACTTGGATGATTGAATGGT TTCCGGATGTGGACTCAGAGCCCACCCTTTCCTGGGAATCTGTGTCTCAGGCCACGAAC TGGACGATCCAGCAAGATAAATTAAAACCTTTCTGGTGCTATAACATCTCTGTGTATCCAAT GTTGCATGACAAAGTTGGCGAGCCATATTCCATCCAGGCTTATGCCAAAGAAGCCGTTCCAT CAGAAGGTCCTGAGACCAAGGTGGAGAACATTGGCGTGAAGACGGTCACGATCACATGGAAA GAGATTCCCAAGAGTGAGAGAAAGGGTATCATCTGCAACTACACCATCTTTTACCAAGCTGA AGGTGGAAAAGGATTCTGTAAGCACGCCCATAGCGAAGTGGAAAAAAACCCCAAGCCCCAGA TAGATGCTATGGATAGACCTGTTGTAGGCATGGCTCCCCCATCTCATTGTGACTTGCAACCT GGGGTTTTGGGGGTTAAATGAGAGTGAAGTGACAGTACCTGAGAGGAGAGTCCTGAGGAAAT GGAAGGAGTTGTTATAATTTGTCCTGGTTAGGCCCTGAATTGACCTCCCGGGAGCTCCCCGA CCATCATTCCCAGGAATGGCGTGCCTGGCTTAAAGAGTGAGGAGGAACAGACCCTGTCACCA TGACTTCTACTGCCCCTGCCAAATCATGCTTTTGTTTTTCAGTCCACCTTATCTCCTGACATCT TAAATACTGGGCAAGGCTTGGATTCTTGCTTAGGCTAAATAATTTTTTCTTATGGTAAAATA CACGTAAAATATTTTTCCAGTTTAAACATTTGAAAGTGTACAATTTAGTGGCATTAGAAGCA TTCACAATATTGTGCAACCATCACCACTATTTCCAGAACTCTTCTATTTCTGCCCAAATAGA AGCCCTATACCCATTCATTAGTCACTCCCCATTCCTCCCCACAGCCCCTGGCAACTAC CAAACTGCTTTGTGTCTCTATGGATTGCCTATTTTGGATATTTCATATACATAGAATCATAA ANTAAAAAAAAAAAAAAAAAAA

Page 207 of 359

WO 02/08288 PCT/US01/21066

94/246

FIGURE 92

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA177313

><subunit 1 of 1, 582 aa, 1 stop

><MW: 66605, pI: 8.14, NX(S/T): 15

MCIROLKFFTTACVCECPONILSPOPSCVNLGMMWTWALWMLPSLCKFSLAALPAKPENI SCVYYYRKNLTCTWSPGKETSYTOYTVKRTYAFGEKHDNCTTNSSTSENRASCSFFLPRI TIPDNYTIEVEAENGDGVIKSHMTYWRLENIAKTEPPKIFRVKPVLGIKRMIOIEWIKPE LAPVSSDLKYTLRFRTVNSTSWMEVNFAKNRKDKNOTYNLTGLOPFTEYVIALRCAVKES KFWSDWSOEKMGMTEEEAPCGLELWRVLKPAEADGRRPVRLLWKKARGAPVLEKTLGYNI WYYPESNTNLTETMNTTNOOLELHLGGESFWVSMISYNSLGKSPVATLRIPAIOEKSFOC IEVMOACVAEDOLVVKWOSSALDVNTWMIEWFPDVDSEPTTLSWESVSOATNWT100DKL KPFWCYNISVYPMLHDKVGEPYSIOAYAKEGVPSEGPETKVENIGVKTVTITWKEIPKSE RKGIICNYTIFYQAEGGKGFCKHAHSEVEKNPKPOIDAMDRPVVGMAPPSHCDLOPGMNH LASLNLSENGAKSTHLLGFWGLNESEVTVPERRVLRKWKELL

Important features of the protein: Signal peptide:

Amino acids

WC0268268 [Be://E-W/00206286 opc]

1-46

N-glycosylation sites:

Amino acids 59-63:69-73:99-103:103-107:125-129:198-202:

215-219;219-223;309-313;315-319;412-416; 427-431;487-491;545-549;563-567

N-mvristovlation sites:

Amino acide 32-38;137-143;483-489;550-556;561-567

Amidation site:

Amino acids 274-278

Growth factor and cytokines receptors family signature 1:

Amino acids

Fibronectin type III domain:

62-75

Amino acids 54-144:154-247

95/246

FIGURE 93

Page 209 of 359

96/246

FIGURE 94

</usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA57700
<subunit 1 of 1, 125 aa, 1 stop
</pre>

<

Important features: Signal peptide: Amino acids 1-21

WCG268268 [Re://E/W/06266286 opc]

N-myristoylation sites: Amino acids 33-39:70-76

Anaphylatoxin domain proteins:

Amino acids 50-60

WO 02/08288

Page 210 of 359

97/246

FIGURE 95

98/246

Page 211 of 359

FIGURE 96

<

Important features: Signal peptide: Amino acids 1-19

WC0208268 [He://E-/W/00206286 opc]

Page 212 of 359

PCT/US01/21066

WC0268268 [Be://E-W/00206286 epc]

WO 02/08288

99/246

FIGURE 97

Page 213 of 359

100/246

FIGURE 98

</usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA62876
<subunit 1 of 1, 120 aa, 1 stop
<kW: 12925, pi: 9.46, NX(S/T): 0
MLPPALPPALVFTVAWSLLAERYSWVRDAEDAHRLOPFVTERTLGKVQRWSGVHTQTGGR
AGGGGFCCAMLDSKRVLASPGWGABNSIKNORVWAPATESSAOLLCCWPYGVARGGALCO</pre>

Important features: Signal peptide: Amino acids 1-17

WCG208268 [Re://E/W/00206286 opc]

N-myristoylation sites: Amino acids 58-64;63-69;64-70;83-89;111-117;115-121

Page 214 of 359

WC0268268 [He://E-W/00206286 opc]

101/246

FIGURE 99

AATTTTTCACCAGAGTAAACTTGAGAAACCAACTGGACCTTGAGTATTGTACATTTTGCCTC GTGGACCCAAAGGTAGCAATCTGAAACATGAGGAGTACGATTCTACTGTTTTGTCTTCTAGG CGGATCAGGGAACACCAACCAACCAGCAGTCAAATCAGGTCTTTCCTTCTTTAAGTCTG ATACCATTAACACAGATGCTCACACTGGGGCCAGATCTGCATCTGTTAAATCCTGCTGCAGG AATGACACCTGGTACCCAGACCCACCCATTGACCCTGGGAGGGTTGAATGTACAACAGCAAC TGCACCCACATGTGTTACCAATTTTTGTCACACACTTGGAGCCCAGGGCACTATCCTAAGC TCAGAGGAATTGCCACAAATCTTCACGAGCCTCATCATCCATTCCTTGTTCCCGGGAGGCAT CCTGCCCACCAGTCAGGCAGGGGCTAATCCAGATGTCCAGGATGGAAGCCTTCCAGCAGGAG GAGCAGGTGTAAATCCTGCCACCCAGGGAACCCCAGCAGGCCGCCTCCCAACTCCCAGTGGC ACAGATGACGACTTTGCAGTGACCACCCCTGCAGGCATCCAAAGGAGCACACATGCCATCGA GGAAGCCACCACAGAATCAGCAAATGGAATTCAGTAAGCTGTTTCAAATTTTTTCAACTAAG CTGCCTCGAATTTGGTGATACATGTGAATCTTTATCATTGATTATATTATGGAATAGATTGA GACACATTGGATAGTCTTAGAAGAAATTAATTCTTAATTTACCTGAAAATATTCTTGAAATTT CAGAAAATATGTTCTATGTAGAGAATCCCAACTTTTAAAAAACAATAATTCAATGGATAAATC TGTCTTTGAAATATAACATTATGCTGCCTGGATGATATGCATATTAAAACATATTTGGAAAA AAAAAAAAAAAAAAAA

Page 215 of 359

102/246

FIGURE 100

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA66660

><subunit 1 of 1, 209 aa, 1 stop

><MW: 21588, pI: 5.50, NX(S/T): 0

MRSTILLFCLIGSTRSLPOLKPALGLPPTKLAPDOGTLPNOQOSNOVFPSLSLIPLTQML TLGPDLHLLNPAAGMTPGTOTHPLTLGGLNVQQOLHPHVLPIFVTQLGAQGTILSSEELP QIFTSLIIHSLFPGGILPTSQAGANPDVQDGSLPAGGAGVNPATQGTPAGRLPTPSGTDD DFAVTTPAGIORSTHAIBEATTESANGIO

Important features of the protein: Signal peptide:

Amino acids 1-16

WC0268268 (Mer//E_W/06Z06286 opc.)

Leucine zipper patterns:

Amino acids 10-32;17-39

N-myristoylation sites:

Amino acids 12-18;25-31;36-42;74-80;108-114;111-117;

135-141;151-157;159-165;166-172;189-195

WC6268368 [Her//E/W/06266286 opc]

WO 02/08288 PCT/US01/21066

Page 216 of 359

103/246

FIGURE 101

ATCCGCAGGTTCCCGCGGACTTGGGGGCCCCGCTGAGCCCCGGCGCCCCGCAGAAGACTTGT GTTTGCCTCCTGCAGCCTCAACCCGGAGGGCCAGCGAGGGCCTACCACCATGATCACTGGTGT AGCGGCGGTGGCCCTGGCCGAGCTGCAGGAGGCCGATGGCCAGTGTCCGGTCGACCGCAGC CTGCTGAAGTTGAAAATGGTGCAGGTCGTGTTTCGACACGGGGCTCGGAGTCCTCTCAAGCC GCTCCCGCTGGAGGAGCAGGTAGAGTGGAACCCCCAGCTATTAGAGGTCCCACCCCAAACTC AGTTTGATTACACAGTCACCAATCTAGCTGGTGGTCCGAAACCATATTCTCCTTACGACTCT CAATACCATGAGACCACCCTGAAGGGGGGCATGTTTGCTGGGCAGCTGACCAAGGTGGGCAT GCAGCAAATGTTTGCCTTGGGAGAGAGACTGAGGAAGAACTATGTGGAAGACATTCCCTTTC TTTCACCAACCTTCAACCCACAGGAGGTCTTTATTCGTTCCACTAACATTTTTCGGAATCTG CCACACTGATGAAGCAGATTCAGAAGTCTTGTATCCCAACTACCAAAGCTGCTGGAGCCTGA GGCAGAGAACCAGAGGCCGGAGGCAGACTGCCTCTTTACAGCCAGGAATCTCAGAGGATTTG AAAAAGGTGAAGGACAGGATGGGCATTGACAGTAGTGATAAAGTGGACTTCTTCATCCTCCT GGACAACGTGCCGAGCAGCACCACCACCTCCCAAGCTGCCCCATGCTGAAGAGATTTG CACGGATGATCGAACAGAGAGCTGTGGACACATCCTTGTACATACTGCCCAAGGAAGACAGG GAAAGTCTTCAGATGGCAGTAGGCCCATTCCTCCACATCCTAGAGAGCAACCTGCTGAAAGC CATGGACTCTGCCACTGCCCCCGACAAGATCAGAAAGCTGTATCTCTATGCGGCTCATGATG TGACCTTCATACCGCTCTTAATGACCCTGGGGATTTTTGACCACAAATGGCCACCGTTTGCT GTTGACCTGACCATGGAACTTTACCAGCACCTGGAATCTAAGGAGTGGTTTGTGCAGCTCTA TTACCACGGGAAGGAGCAGGTGCCGAGAGGTTGCCCTGATGGGCTCTGCCCGCTGGACATGT TCTTGAATGCCATGTCAGTTTATACCTTAAGCCCAGAAAAATACCATGCACTCTGCTCTCAA ${\tt ACTCAGGTGATGGAAGTTGGAAATGAAGAGT{\textbf{AA}}CTGATTTATAAAAGCAGGATGTTGTTGATT}$ TTAAAATAAAGTGCCTTTATACAATG

Page 217 of 359

WO 02/08288

104/246

FIGURE 102

MITGYFSMKIMFPYGUISIANCLHORRVALABLORADOOCPUBSLLKKRWYQVYFRIGARS PLKPLPLEEQV
ENNPOLLEDYP DYTOFDYTWYNLAGGREYSPYDSOYHETKLKGMPAQCIKYCMQQMFALGRERKRYYVEDIF
FLSPTFNPQEVFIRSTNIFFNLESTRCLLAGLPCQORGGFIIIHTDRADSKVLYPNYQSCMSLRQRTRGRROTA
SLQPGISBLUKKYDEMGISSSOKUPFFILLDNVAABCAHHESCHMLKFRAHMEGRAVTVISJYLIKKEDRS
LQMAYGFILHTLESNLLKAMDSATAPDKIRKLYLYABAHDVFFIPLLMYLGIFDHKWPPFAVDLTMELYQHLESK
EFFYCLYYMGREQVFRCOFDGLCPLDMFILMAWYYTLSFEKYHALCSQTQVWEYGNEE

Important features: Signal sequence: amino acids 1-23

cAMP- and cGMP-dependent protein kinase phosphorylation site. amino acids 218-222

Casein kinase II phosphorylation site. amino acids 87-91, 104-108, 320-324

Tyrosine kinase phosphorylation site. amino acids 280-288

N-myristoylation site. amino acids 15-21, 117-123, 118-124, 179-185, 240-246, 387-393

Amidation site. amino acids 216-220

Leucine zipper pattern, amino acids 10-32

Histidine acid phosphatases phosphohistidine signature. amino acids 50--65

Page 218 of 359

WC0268268 [Ber//E_W/06206286 opc]

105/246

FIGURE 103

GGGGCGGTGGACGCGGACTCGAACGCAGTTGCTTCGGGACCCCAGGACCCCCTCGGGCCCGA CCGGGACAGAAGATGTGCTCCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCT GCACTGCCCGCCAGGGGACCACGGTGCCCCGAGACGTGCCACCCGACACGGTGGGGCTGTAC GTCTTTGAGAACGCCATCACCATGCTCGACGCAAGCAGCTTTGCCGGCCTGCCGGGCCTGCA GCTCCTGGACCTGTCACAGAACCAGATCGCCAGCCTGCGCCTGCCCGCCTGCTGCTGG ACCTCAGCCACACAGCCTCCTGGCCCTGGAGCCCGGCATCCTGGACACTGCCAACGTGGAG GCGCTGCGGCTGGTCTGGGGCTGCAGCAGCTGGACGAGGGGCTCTTCAGCCGCTTGCG CAACCTCCACGACCTGGATGTCCCGACAACCAGCTGGAGCGAGTGCCACCTGTGATCCGAG GCCTCCGGGGCCTGACGCCTGCGGCTGGCCGCAACACCCGCATTGCCCAGCTGCGGCCC GAGGACCTGGCCGGCTGCCCTGCAGGAGCTGGATGTGAGCAACCTAAGCCTGCAGGC CCTGCCTGGCGACCTCTCGGGCCTCTTCCCCCGCCTGCGGCTGCTGGCAGCTGCCCGCAACC CCTTCAACTGCGTGTGCCCCTGAGCTGGTTTGGCCCCTGGGTGCGCGAGAGCCACGTCACA CTGGCCAGCCTGAGGAGACGCGCTGCCACTTCCCGCCCAAGAACGCTGGCCGGCTGCTCCT GGAGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACCACCACAGCCACAGTGCCCACCA CGAGGCCCGTGGTGCGGGAGCCCACAGCCTTGTCTTCTAGCTTGGCTCCTACCTGGCTTAGC CCCACAGGGCCGGCCACTGAGGCCCCAGGCCCGCCTCCACTGCCCCACCGACTGTAGGGCC TGTCCCCCAGCCCCAGGACTGCCCACCGTCCACCTGCCTCAATGGGGGCACATGCCACCTGG GGACACGCACCTGGCGTGCTTGTGCCCCGAAGGCTTCACGGGCCTGTACTGTGAGAGC CAGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCACGCCGAGGCCACCACGGTCCCT GACCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGCGTGGGGCTGCAGCGCTACCTCC AGGGGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTATCGCAACCTATCGGGCCCTGAT AAGCGGCTGGTGACGCTGCGTGCCTGCCTCGCTGAGTACACGGTCACCCAGCTGCG AGGAGGCCTGCGGGGAGGCCCATACACCCCCAGCCGTCCACTCCAACCACGCCCCAGTCACC CCCTTGGAGCCAGGCCGAAGGCAACAGAGGCCGTTGGAGAGGCCCTGCCCAGCGGGTCTGA CCTACATCTAAGCCAGAGAGAGACAGGGCAGCTGGGGCCGGGCTCTCAGCCAGTGAGATGGC CAGCCCCTCCTGCTGCCACACCACGTAAGTTCTCAGTCCCAACCTCGGGGATGTGTGCAGA CAGGGCTGTGTGACCACAGCTGGGCCCTGTTCCCTCTGGACCTCGGTCTCCTCATCTGTGAG ATGCTGTGGCCCAGCTGACGAGCCCTAACGTCCCCAGAACCGAGTGCCTATGAGGACAGTGT CCGCCTGCCTCCGCAACGTGCAGTCCCTGGGCACGGCGGCCCTGCCATGTGCTGGTAAC CTCCCGGAAAGAGCAGAGGGAGAGCGGGTAGGCGGCTGTGTGACTCTAGTCTTGGCCCCAGG AAGCGAAGGAACAAAAGAAACTGGAAAGGAAGATGCTTTAGGAACATGTTTTGCTTTTTTAA AATATATATATATATATAAGAGATCCTTTCCCATTTATTCTGGGAAGATGTTTTTCAAACTC AGAGACAAGGACTTTGGTTTTTGTAAGACAAACGATGATATGAAGGCCTTTTGTAAGAAAAA ATAAAAAAAAAAA

Page 219 of 359

106/246

FIGURE 104

</usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA44804
<subunit 1 of 1, 598 aa, 1 stop
<MW: 63030, pI: 7.24, NX(S/T): 3</pre>

WCG268268 (IB#7/E-AV-06206236 opc.)

MCSRVPLLLP.LLLLALGFGYQGCPSGCQCSQPQTVFCTARQGTTVPRDVPPDTVGLYVFEN
GITMLDASSFAGLPGLQLLDLSQNQIASLRLPRLLLLDLSHNSLLALBPGILDTANVEALRL
AGLGLQQLDEGLFSRLRNLHDLDVSDNQLERVPPVIRGLRGLTRLRLAGNTRIAQLRPEDLA
GLAALQELDVSNLSLQALPGDLSGLFPRLRLLAAARNPFNCVCPLSWFGPWVRESHVTLASP
EETRCHFPPKNAGRLLLEDLDVADFGCPATTTTATVFTTPFVVREPTALSSSLAPTWLSPTAP
ATEASPPSTAPPTVGPVQPQDQDCPPSTCLNGGTCHLGTRHLACLCPEGFTGLYCSSQMQQ
GTRPSPTPVTPRPPRSLTLGIEPVSPTSLRVGLQRSVQLRSLRLTYRNLSGFDKRLV
TLRLPASLAETTVTQLRPNATYSVCWMPLGPGKVPEGGEBACGEAHTPPAVHSNHAPVTQARE
GKLPPLLIAPALAAVLLAALAAVGAAYCVRRGRAMAAAAQDKGQVGPGAGPLELEGVKVPLEP
GFKATEGGGEALPSGSEGEVPLMGFPGGLOSPLHAKFYI

Signal sequence.
amino acids 1-23
Transmembrane domain.
amino acids 501-522
N-glycosylation sites.
amino acids 198-202, 425-429, 453-457
Tyrosine kinase phosphorylation site.
amino acids 262-270
N-myristoylation sites.
amino acids 233-29, 27-33, 112-118, 273-279, 519-525, 565-571
Prokaryotic membrane lipoprotein lipid attachment site.
amino acids 14-25
EGF-like domain cysteine pattern signature.
amino acids 353-367

Leucine zipper pattern. amino acids 122-144, 194-216

Page 230 of 359

PCT/US01/21066

WO0268268 [He://E-W/00206286 opc]

WO 02/08288

107/246 FIGURE 105

Page 221 of 359

108/246

FIGURE 106

</user/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA52758
<subunit 1 of 1, 98 aa, 1 stop
<km: 11081, p1: 6.68, NX(s/T): 1
MKLMYLVFTIGLITLLGVQAMPANRISCYRKILKDHNCHNLPEGVADLTQIDVNVQDHFW
DGGGCEMIGYCNFSELLGCPKDVFFGFYEFYFFVDNNQ</pre>

Important features: Signal peptide:

WCG208268 [He://E./W/00206286 opc]

Amino acids 1-20

N-glycosylation site: Amino acids 72-76

Amino acids /2-/6

Tyrosine kinase phosphorylation site:

Amino acids 63-71

WC0268268 [Be://E-W/00206286 epc]

WO 02/08288 PCT/US01/21066

Page 222 of 359

109/246

FIGURE 107

AGTGACTGCAGCCTTCCTAGATCCCCTCCACTCGGTTTCTCTCTTTTGCAGGAGCACCGGCAG CACCAGTGTGTGAGGGGAGCAGGCAGCGGTCCTAGCCAGTTCCTTGATCCTGCCAGACCACC CAGCCCCGGCACAGAGCTGCTCCACAGGCACCATGAGGATCATGCTGCTATTCACAGCCAT TTCCTGGCGGGGGCCGCAGCAAGAGGGATCCAGATCTCTACCAGCTGCTCCAGAGACTCTTC AAAAGCCACTCATCTCTGGAGGGATTGCTCAAAGCCCTGAGCCAGGCTAGCACAGATCCTAA GGAATCAACATCTCCCGAGAAACGTGACATGCATGACTTCTTTGTGGGACTTATGGGCAAGA GGAGCGTCCAGCCAGAGGGAAAGACAGGACCTTTCTTACCTTCAGTGAGGGTTCCTCGGCCC CTTCATCCCAATCAGCTTGGATCCACAGGAAAGTCTTCCCTGGGAACAGAGGAGCAGAGACC TTTATAAGACTCTCCTACGGATGTGAATCAAGAGAACGTCCCCAGCTTTGGCATCCTCAAGTA TCCCCGAGAGCAGAATAGGTACTCCACTTCCGGACTCCTGGACTGCATTAGGAAGACCTCT TTCCCTGTCCCAATCCCCAGGTGCGCACGCTCCTGTTACCCTTTCTCTTCCCTGTTCTTGTA ACATTCTTGTGCTTTGACTCCTTCTCCATCTTTTCTACCTGACCCTGGTGTGGAAACTGCAT AGTGAATATCCCCAACCCCAATGGGCATTGACTGTAGAATACCCTAGAGTTCCTGTAGTGTC CTACATTAAAAATATAATGTCTCTCTATTCCTCAACAATAAAGGATTTTTGCATATGAAA

WO 02/08288

WCG208268 [Re://E/W/00206286 opc]

Page 223 of 359

110/246

FIGURE 108

</user/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA59849
<subunit 1 of 1, 135 aa, 1 stop
<mr: 14833, pI: 9.78, NX(s/T): 0
MRIMLIFTAILAFSLAQSFGAVCKEPQREVVPGGGRSKRDPDLYQLLQRLFKSHSSLEGL
LKALSQASTDPKESTSPEKRDMHDFFVGLMGKRSVQPEGKTGPFLPSVRVPRPLHPNQLG
STGKSSLGTERQRPL</pre>

Important features: Signal peptide: Amino acids 1-18

Tyrosine kinase phosphorylation site: Amino acids 36-45

N-myristoylation sites: Amino acids 33-39;59-65

Amidation site: Amino acids 90-94

Leucine zipper pattern: Amino acids 43-65

Tachykinin family signature:
Amino acids 86-92

WC6268368 [Her//E/W/06266286 opc]

WO 02/08288 PCT/US01/21066

Page 224 of 359

111/246

FIGURE 109

GCGGCCACACGCAGCTAGCCGGAGCCGGACCAGGCGCCTGTGCCTCCTCCTCCTCCTCGC CGCGTCCGCGAAGCCTGGAGCCGGCGGGAGCCCCGCGCTCGCCATGTCGGGCGAGCTCAGCA ACAGGTTCCAAGGAGGGAAGGCGTTCGGCTTGCTCAAAGCCCGGCAGGAGAGGAGGCTGGCC GAGATCAACCGGGAGTTTCTGTGTGACCAGAAGTACAGTGATGAAGAGAACCTTCCAGAAAA GCTCACAGCCTTCAAAGAGAAGTACATGGAGTTTGACCTGAACAATGAAGGCGAGATTGACC TGATGTCTTTAAAGAGGATGATGGAGAAGCTTGGTGTCCCCAAGACCCACCTGGAGATGAAG AAGATGATCTCAGAGGTGACAGGAGGGGTCAGTGACACTATATCCTACCGAGACTTTGTGAA CATGATGCTGGGGAAACGGTCGGCTGTCCTCAAGTTAGTCATGATGTTTGAAGGAAAAGCCA GGACCCCGCCTGGACTCCCCAGCCTTCCCACCCCATACCTCCCGATCTTGCTGCCCTT TCATCAATGTCTTTGTAAAGCACAAATTATCTGCCTTAAAGGGGGCTCTGGGTCGGGGAATCC TGAGCCTTGGGTCCCCTCCTCTTCTTCCCTCCTTCCCCGCTCCCTGTGCAGAAGGGCTG CTCACTTGGAGGAACCAGCACTCTCCATCCTTTCAGAAAGTCTCCAAGCCAAGTTCAGGCTC ACTGACCTGGCTCTGACGAGGACCCCAGGCCACTCTGAGAAGACCTTGGAGTAGGGACAAGG $\tt CTGCAGGGCCTCTTTCGGGTTTCCTTGGACAGTGCCATGGTTCCAGTGCTCTGGTGTCACCC$ AGGACACAGCCACTCGGGGCCCCGCTGCCCCAGCTGATCCCCACTCATTCCACACCTCTTCT CATCCTCAGTGATGTGAAGGTGGGAAGGAAGGAGCTTGGCATTGGGAGCCCTTCAAGAAGG CGTGCAGCCCTACTGTCCCTTACTGGGGCAGCAGAGGGCTTCGGAGGCAGAAGTGAGGCCTG GGGTTTGGGGGGAAAGGTCAGCTCAGTGCTGTTCCACCTTTTAGGGAGGATACTGAGGGGAC CAGGATGGGAGAATGAGGAGTAAAATGCTCACGGCAAAGTCAGCAGCACTGGTAAGCCAAGA

WCocounts (New Androcounts one) Page 205 on 550

WO 02/08288 PCT/US01/21066

112/246

FIGURE 110

MSGELSNRFQGGKAFGLLKARQERRLAEINREFLCDQKYSDEENLPEKLTAFKEKYMEFDLN NEGEIDLMSLKRMMEKLGVPKTHLEMKKMISEVTGGVSDTISYRDFVNMMLGKRSAVLKLVM MFEGKANESSPRPVGPPERDIASLP

Page 235 of 359

WO0268268 [He://E-W/00206286 opc]

113/246

FIGURE 111

Page 227 of 359

114/246 FIGURE 112

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA71290 ><subunit 1 of 1, 85 aa, 1 stop ><MW: 9700, pI: 9.55, NX(S/T): 0 MKKVLLLITAILAVAVGFPVSODOEREKRSISDSDELASGFFVFPYPYPFRPLPPIPFFR FPWFRRNFPIPIPESSPTPLPSSEK

Important features of the protein: Signal peptide: Amino acids 1-17

Amilio acids 1-17

WCG208268 [Re://E/W/00206286 opc]

Homologous region to B3-hordein:

Amino acids 47-85

WC6268368 (Her//E/W/06266286 opc)

WO 02/08288 PCT/US01/21066

Page 228 of 359

115/246

FIGURE 113

CTCCTCTTAACATACTTGCAGCTAAAACTAAATATTGCTGCTTGGGGACCTCCTTCTAGCCT TAAATTTCAGCTCATCACCTTCACCTGCCTTGGTCATGCCTCTCCTTGATCCTT GCCATTTGCACCAGACCTGGATTCCTAGCGTCTCCATCTGGAGTGCGGCTGGTGGGGGGCCT CCACCGCTGTGAAGGGCGGGTGGAGGTGGAACAGAAAGGCCAGTGGGGCACCGTGTGTGATG ACGGCTGGGACATTAAGGACGTGGCTGTGTTGTGCCGGGAGCTGGGCTGTGGAGCTGCCAGC GGAACCCCTAGTGGTATTTTGTATGAGCCACCAGCAGAAAAAGAGCCAAAAGGTCCTCATCCA ATCAGTCAGTTGCACAGGAACAGAAGATACATTGGCTCAGTGTGAGCAAGAAGAAGTTTATG ATTGTTCACATGATGAAGATGCTGGGGCATCGTGTGAGAACCCAGAGAGCTCTTTCTCCCCA GTCCCAGAGGGTGTCAGGCTGGCTGACGCCCTGGGCATTGCAAGGGACGCGTGGAAGTGAA GCACCAGAACCAGTGGTATACCGTGTGCCAGACAGGCTGGAGCCTCCGGGCCGCAAAGGTGG TGTGCCGGCAGCTGGGATGTGGGAGGGCTGTACTGACTCAAAAACGCTGCAACAAGCATGCC TATGGCCGAAAACCCATCTGGCTGAGCCAGATGTCATGCTCAGGACGAGAAGCAACCCTTCA GGATTGCCCTTCTGGGCCTTGGGGGAAGAACACCTGCAACCATGATGAAGACACGTGGGTCG AATGTGAAGATCCCTTTGACTTGAGACTAGTAGGAGGAGACAACCTCTGCTCTGGGCGACTG GAGGTGCTGCACAAGGGCGTATGGGGCTCTGTCTGTGATGACAACTGGGGAGAAAAGGAGGA AATGCTATGGCCCTGGGGTTGGCCGCATCTGGCTGGATAATGTTCGTTGCTCAGGGGAGGAG TGTGGCTGTCATCTGCTCAGTGTAGGTGGGCATCATCTAATCTGTTGAGTGCCTGAATAGAA GAAAAACACAGAAGAAGGGAGCATTTACTGTCTACATGACTGCATGGGATGAACACTGATCT TCTTCTGCCCTTGGACTGGGACTTATACTTGGTGCCCCTGATTCTCAGGCCTTCAGAGTTGG ATCAGAACTTACAACATCAGGTCTAGTTCTCAGGCCATCAGACATAGTTTGGAACTACATCA CCACCTTTCCTATGTCTCCACATTGCACACAGCAGATTCCCAGCCTCCATAATTGTGTGTAT CACCATTTGTCCTGTTTCTCTGAAGAACTCTGACAAAATACAGATTTTGGTACTGAAAGAGA TTCTAGAGGAACGGAATTTTAAGGATAAATTTTCTGAATTGGTTATGGGGTTTCTGAAATTG TATGTGTTCAAA

Page 229 of 359

WO 02/08288

116/246

FIGURE 114

MALIFSLILAICTREGFLASPSGVRLVGGIHRCEGRVEVEQKGQWGTVCDDGWDIKDVAVLC RELGCGAASGTPSGILYEPPAEKEQKVLIGSVSCTGTEDTLAQCEQEEVYDCSHDEDAGASC ENPESSFSVPRGVRLADGGGHRAVL TORRCKHRAYGKREJWLSOMSCSGREATLODCPSGPWGKNTCNHDEDTWVECEDPFDLRLVG GDNLCSGRLEVLHKGVWGSVCDDNWGEKEDQVVCKQLGGGKSLSPSFRDRKCYGPGVGRIWL DNVRCSGEEQSLEQQQHRFWGFHDCTHQEDVAVICSV

Signal sequence:

amino acids 1-15

Casein kinase II phosphorylation site.

amino acids 47-51, 97-101, 115-119, 209-213, 214-218, 234-238, 267-271, 294-298, 316-320, 336-340

N-myristoylation site.

amino acids 29-35, 43-49, 66-72, 68-74, 72-78, 98-104, 137-143, 180-186, 263-269, 286-292

Amidation site.

amino acids 196-200

Speract receptor repeated domain signature.

amino acids 29-67, 249-287

Page 230 of 359

PCT/US01/21066

117/246

WO0268268 [He://E-W/00206286 opc]

WO 02/08288

FIGURE 115

Page 231 of 359

118/246

FIGURE 116

</usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA64896
<subunit 1 of 1, 166 aa, 1 stop
<mm: 19171, pi: 8.26, NX(5/T): 1
MMLHSALGLCLLLYTVSSNLAIAIKKEKRPPOTLSRGWGDDITWVQTYEEGLFYAQKSKK
PLMVIHHLEDCQYSQALKKYFAQNEEIQEMAQNKFIMLNLMHETTDKNLSPDGQYVPRIM
FYDPSITYRADIAGRYSNRLYTYEPRDLPLILENMKKALRUIQSEL</pre>

Important features:
Signal peptide:
Amino acids 1-23

WCG268268 [He://E./W/06266286 opc]

N-myristoylation site: Amino acids 51-57

Page 232 of 359

119/246

WC6268368 [Her//E/W/06266286 opc]

FIGURE 117

CCTGGAGCCGGAAGCGCGGCTGCAGCAGGGCGAGGCTCCAGGTGGGGTCGGTTCCGCATCCA GCCTAGCGTGTCCACGATGCGGCTGGGCTCCGGGACTTTCGCTACCTGTTGCGTAGCGATCG AGAGCGGAACACGGAGCGCCCCAGCGCCCCGAACCCTCGGCTGGAGCCAGTTCTAACTG GACCACGCTGCCACCTCTCTTCAGTAAAGTTGTTATTGTTCTGATAGATGCCTTGAGAG ATGATTTTGTGTTTGGGTCAAAGGGTGTGAAATTTATGCCCTACACAACTTACCTTGTGGAA AAAGGAGCATCTCACAGTTTTGTGGCTGAAGCAAAGCCACCTACAGTTACTATGCCTCGAAT CAAGGCATTGATGACGGGGAGCCTTCCTGGCTTTGTCGACGTCATCAGGAACCTCAATTCTC CTGCACTGCTGGAAGACAGTGTGATAAGACAAGCAAAAGCAGCTGGAAAAAGAATAGTCTTT TATGGAGATGAAACCTGGGTTAAATTATTCCCAAAGCATTTTGTGGAATATGATGGAACAAC CTCATTTTTCGTGTCAGATTACACAGAGGTGGATAATAATGTCACGAGGCATTTGGATAAAG TATTAAAAAGAGGAGATTGGGACATATTAATCCTCCACTACCTGGGGCTGGACCACATTGGC CACATTTCAGGGCCCAACAGCCCCTGATTGGGCAGAAGCTGAGCGAGATGGACAGCGTGCT GATGAAGATCCACACCTCACTGCAGTCGAAGGAGAGAGACGCCTTTACCCAATTTGCTGG TTCTTTGTGGTGACCATGGCATGTCTGAAACAGGAAGTCACGGGGCCTCCTCCACCGAGGAG GTGAATACACCTCTGATTTTAATCAGTTCTGCGTTTGAAAGGAAACCCGGTGATATCCGACA TCCAAAGCACGTCCAATAGACGGATGTGGCTGCGACACTGGCGATAGCACTTGGCTTACCGA CAGTTGAGATTTTTACATTTGAATACAGTGCAGCTTAGTAAACTGTTGCAAGAGAATGTGCC GTCATATGAAAAAGATCCTGGGTTTGAGCAGTTTAAAATGTCAGAAAGATTGCATGGGAACT GGATCAGACTGTACTTGGAGGAAAAGCATTCAGAAGTCCTATTCAACCTGGGCTCCAAGGTT CTCAGGCAGTACCTGGATGCTCTGAAGACGCTGAGCTTGTCCCTGAGTGCACAAGTGGCCCA GTTCTCACCCTGCTCCTGCTCAGCGTCCCACAGGCACTGCACAGAAAGGCTGAGCTGGAAGTC CCACTGTCATCTCCTGGGTTTTCTCTGCTCTTTTATTTGGTGATCCTGGTTCTTTCGGCCGT TCACGTCATTGTGTGCACCTCAGCTGAAAGTTCGTGCTACTTCTGTGGCCTCTCGTGGCTGG CGGCAGGCTGCCTTTCGTTTACCAGACTCTGGTTGAACACCTGGTGTGTGCCAAGTGCTGGC AGTGCCCTGGACAGGGGGCCTCAGGGAAGGACGTGGAGCAGCCTTATCCCAGGCCTCTGGGT GGTTCCTGCGACTGTTACCAAGGTGATTGTAAAGAGCTGGCGGTCACAGAGGAACAAGCCCC CCAGCTGAGGGGGTGTGTGAATCGGACAGCCTCCCAGCAGAGGTGTGGGAGCTGCAGCTGAG GGAAGAAGAGACAATCGGCCTGGACACTCAGGAGGGTCAAAAGGAGACTTGGTCGCACCACT GTTTTCTGTTGGAATTCTTAGTCCTTGGCCTCGGACACCTTCATTCGTTAGCTGGGGAGTGG TGGTGAGGCAGTGAAGAAGAGGCGGATGGTCACACTCAGATCCACAGAGCCCAGGATCAAGG GACCCACTGCAGTGGCAGCAGGACTGTTGGGCCCCCACCCCAACCCTGCACAGCCCTCATCC CCTCTTGGCTTGAGCCGTCAGAGGCCCTGTGCTGAGTGTCTGACCGAGACACTCACAGCTTT GTCATCAGGGCACAGGCTTCCTCGGAGCCAGGATGATCTGTGCCACGCTTGCACCTCGGGCC CATCTGGGCTCATGCTCTCTCCTGCTATTGAATTAGTACCTAGCTGCACACAGTATGTAG TTACCAAAAGAATAAACGGCAATAATTGAGAAAAAAAA

WC-00-88188 (18+1/15 AV-00-2018289 opc.)

WO 02/08288 PCT/US01/21066

Page 233 of 359

120/246

FIGURE 118

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA84920

><subunit 1 of 1, 310 aa, 1 stop

><MW: 33875, pI: 7.08, NX(S/T): 2

MRLGSGTFATCCVÄIEVLGIAVFLRGFFFAPVRSSARAEHGAEPPAPEPSAGASSNWTTL
PPPLFSKVVIVLIDALRDDEVFSSKGVKFMPYTTYLVEKGASHSFVAFAKPETVTMPRIK
ALMTGSLPGFVDVIRNINSPALLEBSVIRQAKAGKRIVFYGDETWYKLFPKHFVEYDGT
TSFFVSDYTEVDNNVTRHLDKVLKRGDWDILILHYLGLDHIGHISGPNSPLIGQKLSEMD
SVLMKIHTSLQSKERETPLPNLLVLCGDHGMSETGSHGASSTEEVNTPLILISSAFERKP
GDIRHPKHVO

Important features of the protein:

Signal peptide:

Amino acids 1-34

Transmembrane domain:

Amino acids 58-76

N-glycosylation sites:

Amino acids 56-60;194-198

N-myristoylation sites:

Amino acids 6-12;52-58;100-106;125-131;233-239;270-276;

275-281;278-284

Amidation site:

Amino acids 154-158

Cell attachment sequence:

Amino acids 205-208

WO0268268 [He://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 234 of 359

121/246

FIGURE 119

GCCACGCGTCCGATGCCGTTCACGTTCGCGGCCTTCTGCTACATGCTGGCGCTGCTCCACATGCTCACATGCTCACATGCTGCTCACATGCTGCTCACATGCTGCTCACATGCTGCTCACATGCTGCTCACATGCTCACATGCTGCTCACATGCTGCTCACATG CTGCCGCGCTCATCTTCTTCGCCATTTGGCACATTATAGCATTTGATGAGCTGAAGACTGAT TACAAGAATCCTATAGACCAGTGTAATACCCTGAATCCCCTTGTACTCCCAGAGTACCTCAT CCACGCTTTCTTGTGTCATGTTTCTTTGTGCAGCAGAGTGGCTTACACTGGGTCTCAATA TGCCCCTCTTGGCATATCATATTTGGAGGTATATGAGTAGACCAGTGATGAGTGGCCCAGGA TGCAAATTAGCTTTTTATCTTCTAGCATTTTTTTACTACCTATATGGCATGATCTATGTTTT AAATGAAGGGATTCTATCCAGCAAGATCCTGTCCAAGAGTAGCCTGTGGAATCTGATCAGTT ACTTTAAAAAATGACTCCTTATTTTTTAAATGTTTCCACATTTTTTGCTTGTGGAAAGACTGT TTTCATATGTTATACTCAGATAAAGATTTTAAATGGTATTACGTATAAATTAATATAAAATG ATTACCTCTGGTGTTGACAGGTTTGAACTTGCACTTCTTAAGGAACAGCCATAATCCTCTGA ATGATGCATTAATTACTGACTGTCCTAGTACATTGGAAGCTTTTGTTTATAGGAACTTGTAG GGCTCATTTTGGTTTCATTGAAACAGTATCTAATTATAAATTAGCTGTAGATATCAGGTGCT TCTGATGAAGTGAAAATGTATATCTGACTAGTGGGAAACTTCATGGGTTTCCTCATCTGTCA TGTCGATGATTATATGGATACATTTACAAAAATAAAAGCGGGAATTTTCCCTTCGCTTG AATATTATCCCTGTATATTGCATGAATGAGAGATTTCCCATATTTCCATCAGAGTAATAAAT ATACTTGCTTTAATTCTTAAGCATAAGTAAACATGATATAAAAATATATGCTGAATTACTTG TGAAGAATGCATTTAAAGCTATTTTAAATGTGTTTTTATTTGTAAGACATTACTTATTAAGA AATTGGTTATTATGCTTACTGTTCTAATCTGGTGGTAAAGGTATTCTTAAGAATTTGCAGGT ACTACAGATTTTCAAAACTGAATGAGAGAAAATTGTATAACCATCCTGCTGTTCCTTTAGTG CAATACAATAAAACTCTGAAATTAAGACTC

Page 235 of 359

WO 02/08288 PCT/US01/21066

122/246

FIGURE 120

<

Important features:
Signal peptide:

Amino acids 1-20

Type II transmembrane domain: Amino acids 11-31

Other transmembrane domain: Amino acids 57-77;123-143

Glycosaminoglycan attachment site: Amino acids 96-100

Page 236 of 359

WC0268268 [Be://E_WO0206286 opc]

123/246

FIGURE 121

CGGACGCGTGGGCGGACGCGTGGGCGGCCCACGGCGCCCGCGGGCTGGGGCGGTCGCTTCTT CCTTCTCCGTGGCCTACGAGGGTCCCCAGCCTGGGTAAAGATGGCCCCATGGCCCCCGAAGG GCCTAGTCCCAGCTGTGCTCTGGGGCCTCAGCCTCTTCCTCAACCTCCCAGGACCTATCTGG CTCCAGCCTCTCCACCTCCCAGTCTTCTCCCCCGCCTCAGCCCCATCCGTGTCATACCTG CCGGGGACTGGTTGACAGCTTTAACAAGGGCCTGGAGAGAACCATCCGGGACAACTTTGGAG GTGGAAACACTGCCTGGGAGGAAGAGATTTGTCCAAATACAAAGACAGTGAGACCCGCCTG GTAGAGGTGCTGGAGGGTGTGCAGCAAGTCAGACTTCGAGTGCCACCGCCTGCTGGAGCT GAGTGAGGAGCTGGTGGAGAGCTGGTGGTTTCACAAGCAGCAGGAGGCCCCGGACCTCTTCC AGTGGCTGTGCTCAGATTCCCTGAAGCTCTGCTGCCCCGCAGGCACCTTCGGGCCCTCCTGC CTTCCCTGTCCTGGGGGAACAGAGGGCCCTGCGGTGGCTACGGGCAGTGTGAAGGAGAAGG GACACGAGGGGCAGCGGCACTGTGACTGCCAAGCCGGCTACGGGGGTGAGGCCTGTGGCC TTTGGCCCCTGTGCCCGATGCTCAGGACCTGAGGAATCAAACTGTTTGCAATGCAAGAAGGG CTGGGCCCTGCATCACCTCAAGTGTGTAGACATTGATGAGTGTGGCACAGAGGGAGCCAACT GTGGAGCTGACCAATTCTGCGTGAACACTGAGGGCTCCTATGAGTGCCGAGACTGTGCCAAG GCCTGCCTAGGCTGCATGGGGGCCAGGCCAGGTCGCTGTAAGAAGTGTAGCCCTGGCTATCA GCAGGTGGGCTCCAAGTGTCTCGATGTGGATGAGTGTGAGACAGAGGTGTGTCCGGGAGAGA ACAAGCAGTGTGAAAACACCGAGGGCGGTTATCGCTGCATCTGTGCCGAGGGCTACAAGCAG ATGGAAGGCATCTGTGTGAAGGAGCAGATCCCAGAGTCAGCAGGCTTCTTCTCAGAGATGAC AGAAGACGAGTTGGTGGTGCTGCAGCAGATGTTCTTTGGCATCATCATCTGTGCACTGGCCA CGCTGGCTGCTAAGGGCGACTTGGTGTTCACCGCCATCTTCATTGGGGCTGTGGCGGCCATG ACTGGCTACTGGTTGTCAGAGCGCAGTGACCGTGTGCTGGAGGGCTTCATCAAGGGCAGA<u>TA</u> ATCGCGGCCACCACCTGTAGGACCTCCTCCCACCCACGCTGCCCCCAGAGCTTGGGCTGCCC TCCTGCTGGACACTCAGGACAGCTTGGTTTATTTTTGAGAGTGGGGTAAGCACCCCTACCTG CCTTACAGAGCAGCCCAGGTACCCAGGCCCGGGCAGACAAGGCCCCTGGGGTAAAAAGTAGC CCTGAAGGTGGATACCATGAGCTCTTCACCTGGCGGGGACTGGCAGGCTTCACAATGTGTGA ATTTCAAAAGTTTTTCCTTAATGGTGGCTGCTAGAGCTTTTGGCCCCTGCTTAGGATTAGGTG GTCCTCACAGGGGTGGGGCCATCACAGCTCCCTCCTGCCAGCTGCATGCTGCCAGTTCCTGT

Page 237 of 359

124/246

FIGURE 122

MAPWPRGLVPAVLWGLSLFIALLFGPTWLQPSPPPGSSPPPQBHPCHTCRGLVDSFNKGLER TIRDNFGGONTAWREBENISKYKDSETRLUFVLEGVCSKSDFSCHRLLELSEBLVESWWFHKO OEAPDLFOWLCSDSLKLCCPAGTFGPSCLPCPGGTERPCGGYQCGEGEGTRGGSGHCDCOAG YGGEACGQCGLGYFEAERNASHLVCSACFGPCARCSGPEESNCLQCKKGWALHHLKCVDIDE CGTEGANGGADQFCVNTTGGYECTCARGXCLGCWGAGPGRCKCSPGYQQVGSKCLDVDECE TEVCPGENKQCENTEGGYECTCARGXKQMSGICVKEQIPESAGFFSEXTEDELVVLQQMFFG IIICALATLAARGDLVFTAITGAVANTGYMLSERSDRVLEGFIKGR

Important features: Signal peptide:

Amino acids 1-29

WC0268268 (Mer//E-/W/06Z06286 opc.)

Transmembrane domain:

Amino acids 342-392

N-glycosylation sites:

Amino acids 79-83;205-209

cAMP- and cGMP-dependent protein kinase phosphorylation site: Amino acids 290-294

Aspartic acid and asparagine hydroxylation site: Amino acids 321-333

EGF-like domain cysteine pattern signature: Amino acids 181-193

Page 238 of 359

WC0268268 [He://E-W/00206286 opc]

125/246

FIGURE 123

 ${\tt GCAAGCCAAGGCGCTGTTTGAGAAGGTGAAGAAGTTCCGGACCCATGTGGAGGAGGGGGACATTGTGTACCGCC}$ TCTACATGCGGCAGACCATCATCAAGGTGATCAAGTTCATCCTCATCATCTGCTACACCGTCTACTACGTGCAC AACATCAAGTTCGACGTGGACTGCACCGTGGACATTGAGAGCCTGACGGCTACCGCACCTACCGCTGTGCCCA CCCCCTGGCCACACTCTTCAAGATCCTGGCGTCCTTCTACATCAGCCTAGTCATCTTCTACGGCCTCATCTGCA TGTACACACTGTGGTGGATGCTACGGCGCTCCCTCAAGAAGTACTCGTTTGAGTCGATCCGTGAGGAGCAGC TACAGCGACATCCCCGACGTCAAGAACGACTTCGCCTTCATGCTGCACCTCATTGACCAATACGACCCGCTCTA GGACGCTGGACAAGCTCCGGCAGCGGCTCACCAAGAACGCGCAGGACAAGCTGGAGCTGCACCTGTTCATGCTC AGTGGCATCCCTGACACTGTTTTGACCTGGTGGAGCTGGAGGTCCTCAAGCTGGAGCTGATCCCCGACGTGAC CATCCCGCCCAGCATTGCCCAGCTCACGGGCCTCAAGGAGCTGTGGCTCTACCACACACGCGGCCAAGATTGAAG CGCCTGCGCTGGCCTTCCTGCGCGAGAACCTGCGGGCGCTGCACATCAAGTTCACCGACATCAAGGAGATCCCG CTGTGGATCTATAGCCTGAAGACACTGGAGGAGCTGCACCTGACGGGCAACCTGAGCGCGGAGAACAACCGCTA CACAGGTGGTCACAGATCTGGGCGTGCACCTGCAGAAGCTGTCCATCAACAATGAGGGCACCAAGCTCATCGTC CTCAACAGCCTCAAGAAGATGGCGAACCTGACTGAGCTGAGCTGATCCGCTGCGACCTGGAGCGCATCCCCCA CTCCATCTTCAGCCTCCACAACCTGCAGGAGATTGACCTCAAGGACAACAACCTCAAGACCATCGAGGAGATCA TCAGCTTCCAGCACCTGCACCTCACCTGCCTTAAGCTGTGGTACAACCACATCGCCTACATCCCCATCCAG CTACTGCCGCAAGCTGCGCTACCTGGACCTCAGCCACAACAACCTGACCTTCCTCCCTGCCGACATCGGCCTCC AAGCTGCGGGCCCTGCACCTGGGCAACAACGTGCTGCAGTCACTGCCCTCCAGGGTGGGCGAGCTGACCAACCT GACGCAGATCGAGCTGCGGGGCAACCGGCTGGAGTGCCTGCTGTGGAGCTGGGCGAGTGCCCACTGCTCAAGC GCAGCGGCTTGGTGGTGGAGGAGGACCTGTTCAACACACTGCCACCCGAGGTGAAGGAGCGGCTGTGGAGGGCT GACAAGGAGCAGGCCTGAGCGAGGCCGGCCCAGCACAGCAGCAGCAGGACCGCTGCCCAGTCCTCAGGCCCGG AGGGGCAGGCCTAGCTTCTCCCAGAACTCCCGGACAGCCAGGACAGCCTCGCGGCTGGGCAGGAGCCTGGGGCC GCTTGTGAGTCAGGCCAGAGCGAGAGGACAGTATCTGTGGGGCCTGGCCCCTTTTCTCCCTCTGAGACTCACGTC CCCCAGGGCAAGTGCTTGTGGAGGAGAGCAAGTCTCAAGAGCGCAGTATTTGGATAATCAGGGTCTCCTCCCTG GAGGCCAGCTCTGCCCCAGGGGCTGAGCTGCCACCAGAGGTCCTGGGACCCTCACTTTAGTTCTTGGTATTTAT TTTTCTCCATCTCCCACCTCCTTCATCCAGATAACTTATACATTCCCAAGAAAGTTCAGCCCAGATGGAAGGTG ACTTCAGCAGAGTGGTCCGGGGCGAACCAGCCATGGGACGGTCACCCAGCAGTGCCGGGCTGGGCTCTGCGGTG CGGTCCACGGGAGAGCAGGCCTCCAGCTGGAAAGGCCAGGCCTGGAGCTTGCCTCTTCAGTTTTTGTGGCAGTT GTGGCAGTTTCCCTTGAGCAAGCAGCCAGACGTTGAACTGTGTTTCCTTTCCCTGGGCGCAGGGTGCAGGGTG CAGAGGGAATGTTCTGGAGCTGCCAAGGAGGAGGAGAGCTCGGGTTGGCTAATCCCCGGATGAACGGTGCTCCA TTCGCACCTCCCTCCTCGTGCCTGCCTCTCCACGCACACTGTTAAGGAGCCAAGAGGAGCCACTTCGC CCAGACTTTGTTTCCCCACCTCCTGCGGCATGGGTGTCCAGTGCCACCGCTGGCCTCCGCTGCTTCCATCAG CCCTGTCGCCACCTGGTCCTTCATGAAGAGCAGACACTTAGAGGCTGGTCGGGAATGGGGAGGTCGCCCCTGGG AGGGCAGGCGTTGGTTCCAAGCCGGTTCCCGTCCCTGGCGCCTGGAGTGCACACAGCCCAGTCGGCACCTGGTG GCGTCGTGTCATTGGATATAATCCTCAGAAATAATGCACACTAGCCTCTGACAACCATGAAGCAAAAATCCGTT

Page 239 of 359

126/246

FIGURE 124

MRQTIIKVIKFILIICYTVYYVHNIKFDVDCTVDIBSLTGYRTYRCAHPLATLFKILASFYI
SLVIFYGLICMYTLWMMLRRSLKKYSFESIREESSYSDIPDVKNDFAFMLHLIDQYDPLYSK
RFAVFLSEVSENKLRQIMLNNEWTLDKLRQRITKNAQDKLELHLFMLSGIPDTVFDLVELEV
LKLELIPDVTIPPSIAQLTGLKELWILHTAAKIEAPALAFLRENLRALHIKFTDIKEIPLWI
YSLKTLEELHLTGNLSAENNRYIVIDGLRELKRLKVLRLKSNLSKLPQVVTDVGVHLQKLSI
NNEGTKLIVLNSLKKMANLTELELIRCDLERIPHSIFSLHNLQEIDLKDNNLKTIEBIISFG
HLHRITCLKLWYNHTAYIPIOIGNLTMLERLYINRKKIEKIPTQLFYCRKLRYLDLSHNNLT
FLPADIGLLQNLQNLAITANRIETLPPELFQCRKLRALHLGNNVLQSLPSRVGELTNLTQIE
LRCNRLECLPVELGECPLLKRSGLVVEEDLFNTLPPEVKERLWRADKEQA

Transmembrane domain:

WC0268268 (Mer//E-/W/06/206286 opc.)

amino acids 51-75 (type II)

N-glycosylation site.

amino acids 262-266, 290-294, 328-332, 396-400, 432-436, 491-495

cAMP- and cGMP-dependent protein kinase phosphorylation site. amino acids 85-89

Casein kinase II phosphorylation site.

amino acids 91-95, 97-101, 177-181, 253-257, 330-334, 364-368, 398-402, 493-497

N-myristoylation site.

amino acids 173-179, 261-267, 395-401, 441-447

Page 240 of 359

WO 02/08288 PCT/US01/21066

127/246

WC6268368 [Her//E/W/06266286 opc]

FIGURE 125

GTTGTGTCCTTCAGCAAAACAGTGGATTTAAATCTCCTTGCACAAGCTTGAGAGCAACAACACAA TCTATCAGGAAAGAAAGAAAAAACCGAACCTGACAAAAAAGAAGAAAAAGAAGAAGAAGA AAAAAAATCATGAAAACCATCCAGCCAAAAATGCACAATTCTATCTCTTGGGCAATCTTCAC GGGGCTGGCTGTGTGTCTCCCAAGGAGTGCCCGTGCGCAGCGGAGATGCCACCTTCC CCAAAGCTATGGACAACGTGACGGTCCGGCAGGGGGAGAGCGCCACCCTCAGGTGCACTATT GACAACCGGGTCACCCGGGTGGCCTGGCTAAACCGCAGCACCATCCTCTATGCTGGGAATGA CAAGTGGTGCCTGGATCCTCGCGTGGTCCTTCTGAGCAACCCCAAACGCAGTACAGCATCG CACCCAAAGACCTCTAGGGTCCACCTCATTGTGCAAGTATCTCCCAAAATTGTAGAGATTTC TTCAGATATCTCCATTAATGAAGGGAACAATATTAGCCTCACCTGCATAGCAACTGGTAGAC GAATACTTGGAAATTCAGGGCATCACCCGGGAGCAGTCAGGGGACTACGAGTGCAGTGCCTC CANTGACGTGGCCGCGCCGTGGTACGGAGGTAAAGGTCACCGTGAACTATCCACCATACA TTTCAGAAGCCAAGGGTACAGGTGTCCCCGTGGGACAAAAGGGGACACTGCAGTGTGAAGCC TCAGCAGTCCCCTCAGCAGAATTCCAGTGGTACAAGGATGACAAAAGACTGATTGAAGGAAA GAAAGGGGTGAAAGTGGAAAACAGACCTTTCCTCTCAAAACTCATCTTCTAATGTCTCTG AACATGACTATGGGAACTACACTTGCGTGGCCTCCAACAAGCTGGGCCACACCAATGCCAGC ATCATGCTATTTGGTCCAGGCGCCGTCAGCGAGGTGAGCAACGGCACGTCGAGGAGGGCAGG CTGCGTCTGGCTGCTCTTCTGGTCTTGCACCTGCTTCTCAAATTT**TGA**TGTGAGTGCC CGACAGCAACCAATCAGATATATACAAATGAAATTAGAAGAACACAGCCTCATGGGACAGA AATTTGAGGGAGGGAACAAAGAATACTTTGGGGGGAAAAGAGTTTTAAAAAAAGAAATTGAA AATTGCCTTGCAGATATTTAGGTACAATGGAGTTTTCTTTTTCCCAAACGGGAAGAACACAGC ACACCGGCTTGGACCCACTGCAAGCTGCATCGTGCAACCTCTTTGGTGCCAGTGTGGGCAA GGGCTCAGCCTCTCTGCCCACAGAGTGCCCCCACGTGGAACATTCTGGAGCTGGCCATCCCA AATTCAATCAGTCCATAGAGACGAACAGAATGAGACCTTCCGGCCCAAGCGTGGCGCTGCGG GCACTTTGGTAGACTGTGCCACCACGGCGTGTGTTGTGAAACGTGAAATAAAAAGAGCAAAA AAAAA

Page 241 of 359

128/246

FIGURE 126

MKYIQPKMHNSISWAIFTGLAALCLFQGYPVRSGDATFPKAMDNYTVRQGESATLRCTIDNR VTRVAWLNRSTILYAGNDKWCLDPRVVLLSNTQTQYSIBIQNVDYYDGEPYTCSVQTDHPK TSRVHLIVQVSPKIVBISSDISINBGNNISLTCIATGRPEPTVTWRHISPKAVGFVSEDBYL EIQGITREQSGDYBCSASNDVAAPVVRRVKVTVNYPPYISEAKGTGVPVGQKGTLQCEASAV PSAEFQWYKDDKRLIEGKKGVKVENRFFLSKLIFFNVSEHDYGNYTCVASNKLGHTNASIML FGPGAYSEVSNGTSRRAGCVWLLPLLVLHLLLKF

Important features: Signal peptide: amino acids 1-28

WCG268268 [IB#1//E/W/06206236 opc.]

129/246

FIGURE 127

GCCCCAACCCCGCCCCCCCCCTAGCCCCCCGCGCCCGCGCCCCGCGCCCCAGGTGAGCGCTCCG CGTCAAACCACCTGATCCCATAAAACATTCATCCTCCCGGCGGCCCGCGCTGCGAGCGCCCCGCCAGTCCGCCC GCCGCGGGGAGACGGGCGCCCGCAAACGACTTTCAGTCCCCGACGCCCCCCAACCCCTACGATGAA GAGGCCTCCGCTGGAGGGAGCCGCTGCTGGCATGGTTGCTGTGCTGCAGGCCTGGCAGGTGGCAGCCCCAT GCCCAGGTGCCTGCGTATGCTACAATGAGCCCAAGGTGACGACAAGCTGCCCCCAGCAGGGCCTGCAGGCTGTG CCCGTGGGCATCCCTGCCAGCCAGCCATCTTCCTGCACGGCAACCGCATCTCGCATGTGCCAGCTGCCAG CTTCCGTGCCTGCCGCAACCTCACCATCCTGTGGCTGCACTCGAATGTGCTGGCCCGAATTGATGCGGCTGCCT TCACTGGCCTGGCCCTCCTGGAGCAGCTGGACCTCAGCGATAATGCACAGCTCCGGTCTGTGGACCCTGCCACATTCCACGGCCTGGGCCGCCTACACACGCTGCACCTGGACCGCTGCGGCCTGCAGGAGCTGGGCCCGGGGCTGTT CCGCGGCCTGGCTGCCCTGCAGTACCTCTACCTGCAGGACACGCGCTGCAGGCACTGCCTGATGACACCTTCC GCGACCTGGGCAACCTCACACACCTCTTCCTGCACGGCAACCGCATCTCCAGCGTGCCCGAGCGCGCCTTCCGT GGGCTGCACAGCCTCGACCGTCTCCTACTGCACCAGAACCGCGTGGCCCATGTGCACCCGCATGCCTTCCGTGA CCTTGGCCGCCTCATGACACTCTATCTGTTTGCCAACAATCTATCAGCGCTGCCCACTGAGGCCCTGGCCCCCC TGCGTGCCCTGCAGTACCTGAGGCTCAACGACACCCCTGGGTGTGTGACTGCCGGGCACGCCCACTCTGGGCC CAAACGCCTAGCTGCCAATGACCTGCAGGGCTGCGCTGTGGCCACCGGCCCTTACCATCCCATCTGGACCGGCA GAGCCTGGAAGACCAGCTTCGGCAGGCAATGCGCTGAAGGGACGCGTGCCGCCCGGTGACAGCCCGCCGGGCAA CAGTGCGCCCGAGGGCTCCGAGCCACCAGGGTTCCCCACCTCGGGCCCTCGCCGGAGGCCAGGCTGTTCACGC CTCAGGTGCCCTACCCAGCCTCACCTGCAGCCTCACCCCCTGGGCCTGGTGCTGTGGACAGTGCTTG $\tt CGCCGCCA\overline{AGC}CAGCCGGGCGGCCGACCCGTGGGGCCAGGCCAGGTCCTCCCTGATGGACGCCTGCCGCCCGGCCAGGCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCCAGGCAGGC$ CGCCACCCCATCTCCCACCCCATCATGTTTACAGGGTTCGGCGGCAGCGTTTGTTCCAGAACGCCGCCTCCCAC CCAGATCGCGGTATATAGAGATATGCATTTTATTTTACTTGTGTAAAAATATCGGACGACGTGGAATAAAGAGC TCTTTTCTTAAAAAAA

Page 243 of 359

130/246

FIGURE 128

MKRASAGGSRLLAWVLWLQAWQVAAPCPGACVCYNEPKVTTSCPOOGLQAVPVGIPAASQRIFLHGNRISHVPA ASFRACRNLTILWLHSNVLARIDAAAFTGLALLEQLDLSDNAQLRSVDPATFHGLGRLHTLHLDRCGLQELGPG LFRGLAALQYLYLQDNALQALPDDTFRDLGNLTHLFLHGNRISSVPERAFRGLHSLDRLLLHQNRVAHVHPHAF RDLGRLMTLYLFANNLSALPTEALAPLRALOYLRLNDNPWVCDCRARPLWAWLOKFRGSSSEVPCSLPORLAGR DLKRLAANDLQGCAVATGPYHPIWTGRATDEEPLGLPKCCQPDAADKASVLEPGRPASAGNALKGRVPPGDSPP GNGSGPRHINDSPFGTLPGSAEPPLTAVRPEGSEPPGFPTSGPRRRPGCSRKNRTRSHCRLGQAGSGGGGTGDS EGSGALPSLTCSLTPLGLALVLWTVLGPC

Important features: Signal peptide: amino acids 1-26

WC0268268 [Be://E-W/00206286 opc]

Leucine zipper pattern. amino acids 135-156

Glycosaminoglycan attachment site. amino acids 436-439

N-glycosylation site. amino acids 82-85, 179-183, 237-240, 372-375 and 423-426

VWFC domain amino acids 411-425

Page 244 of 359

WO 02/08288 PCT/US01/21066

131/246

WO0268268 [He://E-W/00206286 opc]

FIGURE 129

GCGCCGGGAGCCCATCTGCCCCCAGGGGCACGGGGCGCGGGGCCGGCTCCCGGCCCGGCACATGGCTGCAGCCAC CTCGCGCGCACCCCGAGGCGCCGCCCCAGCTCGCCGAGGTCCGTCGGAGGCCGCCCGGCCGCCCGGAGCCAA GCAGCAACTGAGCGGGGAAGCGCCCGCGTCCGGGGATCGGG<u>ATC</u>TCCCTCCTCCTTCTCCTCTTGCTAGTTTCC TACTATGTTGGAACCTTGGGGACTCACACTGAGATCAAGAGGTGGCAGAGGAAAAGGTCACTTTGCCCTGCCA CCATCAACTGGGGCTTCCAGAAAAAGACACTCTGGATATTGAATGGCTGCTCACCGATAATGAAGGGAACCAAA AAGTGGTGATCACTTACTCCAGTCGTCATGTCTACAATAACTTGACTGAGGAACAGAAGGGCCCGAGTGGCCTTT GCTTCCAATTTCCTGGCAGGACATGCCTCCTTGCAGATTGAACCTCTGAAGCCCAGTGATGAGGGCCGGTACAC CTGTAAGGTTAAGAATTCAGGGCGCTACGTGTGGAGCCATGTCATCTTAAAAGTCTTAGTGAGACCATCCAAGC CCAAGTGTGAGTTGGAAGGAGCTGACAGAAGGAAGTGACCTGACTTTGCAGTGTGAGTCATCCTCTGGCACA GAGCCCATTGTGTATTACTGGCAGCGAATCCGAGAGAAAGAGGGAGAGGATGAACGTCTGCCTCCCAAATCTAG GATTGACTACAACCACCCTGGACGAGTTCTGCTGCAGAATCTTACCATGTCCTACTCTGGACTGTACCAGTGCA CAGCAGGCAACGAAGCTGGGAAGGAAGCTGTGTGCTGCGAGTAACTGTACAGTATGTACAAAGCATCGGCATG GTTGCAGGAGCAGTGACAGGCATAGTGGCTGGAGCCCTGCTGATTTTCCTCTTGGTGTGGCTGCTAATCCGAAG GAAAGACAAAGAAAGATATGAGGAAGAAGAGAGACCTAATGAAATTCGAGAAGATGCTGAAGCTCCAAAAGCCC GTCTTGTGAAACCCAGCTCCTCTCCTCAGGCTCTCGGAGCTCACGCTCTGGTTCTTCCTCCACTCGCTCCACA ATACAGCCTAGTGGGGCCAGAGTGAGAGGTTCTGAACCAAAGAAGTCCACCATGCTAATCTGACCAAAGCAG AAACCACACCAGCATGATCCCCAGCCAGAGCAGAGCCTTCCAAACGGTCTGAATTACAATGGACTTGACTCCC ACGCTTTCCTAGGAGTCAGGGTCTTTGGACTCTTCTCGTCATTGGAGCTCAAGTCACCAGCCACACAACCAGAT GAGAGGT CATCT AAGTAGCAGTGAGCATTGCACGGAACAGATT CAGATGAGCATTTT CCTTATACAATACCAAA CAAGCAAAAGGATGTAAGCTGATTCATCTGTAAAAAGGCATCTTATTGTGCCTTTAGACCAGAGTAAGGGAAAG CAGGAGTCCAAATCTATTTGTTGACCAGGACCTGTGGTGAGAAGGTTGGGGGAAAGGTGAGGTGAATATACCTAA AACTTTTAATGTGGGATATTTTGTATCAGTGCTTTGATTCACAATTTTCAAGAGGAAATGGGATGCTGTTTGTA AATTTTCTATGCATTTCTGCAAACTTATTGGATTATTAGTTATTCAGACAGTCAAGCAGACCCACAGCCTTAT TACACCTGTCTACACCATGTACTGAGCTAACCACTTCTAAGAAACTCCAAAAAAGGAAACATGTGTCTTCTATT CTGACTTAACTT CATTTGTCATAAGGTTTGGATATTAATTTCAAGGGGAGTTGAAATAGTGGGAGATGGAGAAG AGTGAATGAGTTTCTCCCACTCTATACTAATCTCACTATTTGTATTGAGCCCAAAATAACTATGAAAGGAGACA AAAATTTGTGACAAAGGATTGTGAGAGGCTTTCCATCTTCATGATGTTATGAGGATTGTTGACAAACATTAGAA ATATATATGGAGCAATTGTGGATTTCCCCTCAAATCAGATGCCTCTAAGGACTTTCCTGCTAGATATTTCTGG GCTGAAAGATTACCCAACATACCATTATAGTCTCTTCTTCTTGAGAAAATGTGAAACCAGAATTGCAAGACTGG CCTGTAGGAAAATCCAGCAGGTGGAGGTTGCAGTGAGCCGAGATTATGCCATTGCACTCCAGCCTGGGTGACAG AGCGGGACTCCGTCTC

Page 245 of 359

132/246

FIGURE 130

MSLILLILLVSYYVGLIGTHTELKKYABEKYTLPCHGJGLPEKDTLDIEWLLTDNIGGOKVVITYSSRHYNN
LTEEDKGRVAFASNFLAGDASLQIEPLKPSDEGYTCKYMSGRYVWSHYLLKVLVRPSKPKCELEGELTEGSD
LTLQCSSSGTEFIVYTWGKIREKEGEDERLPFRSRIDYNHFGRVLLQNLTHSYSGLTYCTANNEAGRESCVVR
VTVQVVQSIGWYAGAVTGIVAGALLIFLJWHLLIRKDKDEKYEEEERRWBITENDAERARLVKFSSSSGSRS
SSGSSSTSTANSASSRORTLETDAAPQGEJATQYSLVOPEVGGSEPKKVHHANLTKAFTTPSMTPAGNAFQVT

Important freatures: Signal sequence: amino acids 1-16

WO0268268 [He://E-W/00206286 opc]

Transmembrane domain: amino acids 232-251

Page 246 of 359

WCG268268 (IB#7/E-AVO6206286 opc.)

133/246

FIGURE 131

GGAAGTCCACGGGGAGCTTGGATGCCAAAGGGAGGACGGCTGGGTCCTCTGGAGAGGACTAC TCACTGGCATATTTCTGAGGTATCTGTAGAATAACCACAGCCTCAGATACTGGGGACTTTAC AGTCCCACAGAACCGTCCTCCCAGGAAGCTGAATCCAGCAAGAACAATGGAGGCCAGCGGGA AGCTCATTTGCAGACAAAGGCAAGTCCTTTTTTCCTTTCTCCTTTTGGGCTTATCTCTGGCG GGCGCGGCGGAACCTAGAAGCTATTCTGTGGTGGAGGAAACTGAGGGCAGCTCCTTTGTCAC CAATTTAGCAAAGGACCTGGGTCTGGAGCAGAGGGAATTCTCCAGGCGGGGGTTAGGGTTG TTTCCAGAGGGAACAACTACATTTGCAGCTCAATCAGGAGACCGCGGATTTGTTGCTAAAT GAGAAATTGGACCGTGAGGATCTGTGCGGTCACACAGAGCCCTGTGTGCTACGTTTCCAAGT GTTGCTAGAGAGTCCCTTCGAGTTTTTTCAAGCTGAGCTGCAAGTAATAGACATAAACGACC ACTCTCCAGTATTTCTGGACAAACAAATGTTGGTGAAAGTATCAGAGAGCAGTCCTCCTGGG ACTACGTTTCCTCTGAAGAATGCCGAAGACTTAGATGTAGGCCAAAACAATATTGAGAACTA TATAATCAGCCCCAACTCCTATTTTCGGGTCCTCACCCGCAAACGCAGTGATGGCAGGAAAT ACCCAGAGCTGGTGCTGGACAAAGCGCTGGACCGAGAGAAGAAGCTGAGCTCAGGTTAACA CTCACAGCACTGGATGGTGGCTCTCCGCCCAGATCTGGCACTGCTCAGGTCTACATCGAAGT CCTGGATGTCAACGATAATGCCCCTGAATTTGAGCAGCCTTTCTATAGAGTGCAGATCTCTG AGGACAGTCCGGTAGGCTTCCTGGTTGTGAAGGTCTCTGCCACGGATGTAGACACAGGAGTC AACGGAGAGATTTCCTATTCACTTTTCCAAGCTTCAGAAGAGATTGGCAAAACCTTTAAGAT CAATCCCTTGACAGGAGAAATTGAACTAAAAAAACAACTCGATTTCGAAAAACTTCAGTCCT ATGAAGTCAATATTGAGGCAAGAGATGCTGGAACCTTTTCTGGAAAATGCACCGTTCTGATT CAAGTGATAGATGTGAACGACCATGCCCCAGAAGTTACCATGTCTGCATTTACCAGCCCAAT ACCTGAGAACGCGCCTGAAACTGTGGTTGCACTTTTCAGTGTTTCAGATCTTGATTCAGGAG AAAATGGGAAAATTAGTTGCTCCATTCAGGAGGATCTACCCTTCCTCCTGAAATCCGCGGAA AACTTTTACACCCTACTAACGGAGAGACCACTAGACAGAGAAAGCAGAGCGGAATACAACAT CACTATCACTGTCACTGACTTGGGGACCCCTATGCTGATAACACAGCTCAATATGACCGTGC TGATCGCCGATGTCAATGACAACGCTCCCGCCTTCACCCAAACCTCCTACACCCTGTTCGTC CACCAACGCCAGGTCACCTACTCGCTGCTGCCCCCAGGACCCGCACCTGCCCCTCACAT CCCTGGTCTCCATCAACGCGGACAACGGCCACCTGTTCGCCCTCAGGTCTCTGGACTACGAG GCCCTGCAGGGGTTCCAGTTCCGCGTGGGCGCTTCAGACCACGGCTCCCCGGCGCTGAGCAG CGAGGCGCTGGTGCGCGTGGTGCTGGACGCCAACGACAACTCGCCCTTCGTGCTGTACC CGCTGCAGAACGGCTCCGCGCCCTGCACCGAGCTGGTGCCCCGGGCGGCCGAGCCGGGCTAC CTGGTGACCAAGGTGGTGGCGGTGGACGCGACTCGGGCCAGAACGCCTGGCTGTCGTACCA GCTGCTCAAGGCCACGGAGCTCGGTCTGTTCGGCGTGTGGGCGCACAATGGCGAGGTGCGCA CCGCCAGGCTGCTGAGCGAGCGCGACGCCGAGCACAGCTGGTGGTGCTGGTCAAGGAC AATGGCGAGCCTCCGCGCCACCGCCACGCTGCACGTGCTCCTGGTGGACGGCTTCTC CCAGCCCTACCTGCCTCTCCCGGAGGCGGCCCCGACCCAGGCCCAGGCCGACTTGCTCACCG TCTACCTGGTGGTGGCGTTGGCCTCGGTGTCTTCGCTCTTTTCGGTGCTCCTGTTC GTGGCGGTGCGCTGTGTAGGAGGAGCAGGCCGCCTCGGTGGGTCGCTGCTTGGTGCCCGA GGGCCCCTTCCAGGGCATCTTGTGGACATGAGCGCACCAGGACCCTATCCCAGAGCTACC AGTATGAGGTGTGTCTGGCAGGAGGCTCAGGGACCAATGAGTTCAAGTTCCTGAAGCCGATT ATCCCCAACTTCCCTCCCAGTGCCCTGGGAAAGAAATACAAGGAAATTCTACCTTCCCCAA TAACTTTGGGTTCAATATTCAGTGACCATAGTTGACTTTTACATTCCATAGGTATTTTATTT TTACTCTTGATTTTTCTCATGTTCTTCTCCCTTTGTTTTAAAGTGAACATTTACCTTTATT CCTGGTTCTT

Page 247 of 359

134/246

</usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA48314</pre>

FIGURE 132

<subunit l of 1, 798 aa, 1 stop

<mi: 87552, pi: 4.84, NX(S/T): 5

MEASCKLICRORQVLFSFLLIGLSLAGAAEPRSYSVVEETEGSSFVTNLAKDLGLEQREFSR
RGVRVVSRGNKLHLQLNQETADLLLNEKLDREDLCCHTEPCVLREQVLLESPFFFFCAELQV
DIDNDSFYPLDKCMLVKVSESSPPGTTFPLKNABLDUVGONNIENTYISPNSYFRVLTRKR
SDGRKYPELVLDKALDREERAELSLTLTALDGGSPPRSGTAQVYIEVLDVNDNAPEFEQPFY
RVQISEDSPVGFLVVKVSATDVDTGVNGEISYSLFQASEEIGKTFKINPLTGEIELKKQLDF
EKLQSYEVNIEARDAGTFSGKCTVLIQVIDVNDHAPEVTMSAFTSFIPENAPETVVALFSVS
DLDSGENGKISCSIQEDLPFLLKSAEMFYTLLTERFLDRESRAEVNITITVTDLGTPMLTQ
LINTVLIADVNDNAPAFTOTSYTLFVENNSPALHTRSVSATDRSGTNAQVYTSLLPPQDP
HLPLTSLVSINADNGHLFALRSLDYEALQGFQFRVGASDHGSFALSSEALVRVVVLDANDNS
PFVLYPLQNGSAPCTELVPRAAEPGYLVTKVVAVDGDSGQNAWLSYQLLKATELGLFGVWAH
NGEVRTARLLSERDAAKHRLVVLVKONGEPPRSATATLEVLLVDGFSQPYLPLEAAPTOAQ
ADLLTYYLVVALASVSSLFLFSVLLFYAVRLCRRSRAASVGCLVPEGPLFGHLVDMSGTRT
LSQSYQYEVCLAGGSGTNEFFKFLKPITPNFPPQCFKETQGNSTPNNFGFNIG</pre>

Important features: Signal peptide: amino acids 1-26

WC0268268 [Be://E-W/00206286 opc]

Transmembrane domain: amino acids 685-712

Cadherins extracellular repeated domain signature. amino acids 122-132, 231-241, 336-346, 439-449 and 549-559

ATP/GTP-binding site motif A (P-loop). amino acids 285-292

N-glycosylation site. amino acids 418-421, 436-439, 567-570 and 786-789

Page 248 of 359

PCT/US01/21066

135/246

WCG268268 (IB#7/E-AV-06206236 opc.)

WO 02/08288

FIGURE 133

GGAAGGGGAGGAGCAGGCCACACAGGCCACAGGCCGGTGAGGGACCTGCCCAGACCTGGAGGGTCTCGCTCTGTC ACACAGGCTGGAGTGCAGTGGTGATCTTGGCTCATCGTAACCTCCACCTCCCGGGTTCAAGTGATTCTCATG CAGTCGCTGCTGCAGACGACACTGTTCCTGCTGAGTCTGCTCCTGGTCCAAGGTGCCCACGGCAGGGGCCA CAGGGAAGACTTTCGCTTCTGCAGCCAGCGGAACCAGACACAGGGGGCAGCCTCCACTACAAACCCACACCAG ACCTGCGCATCTCCATCGAGAACTCCGAAGAGCCCTCACAGTCCATGCCCCTTTCCCTGCAGCCCACCCTGCT TCCCGATCCTTCCCTGACCCCAGGGGCCTCTACCACTTCTGCCTCTACTGGAACCGACATGCTGGGAGATTACA TCTTCTCTATGGCAAGCGTGACTTCTTGCTGAGTGACAAAGCCTCTAGCCTCCTCTCCTCCAGCACCAGGAGG AGAGCCTGGCTCAGGGCCCCCCCCTGTTAGCCACTTCTGTCACCTCCTGGTGGAGCCCTCAGAACATCAGCCTG CCCAGTGCCGCCAGCTTCACCTTCTCCTTCCACAGTCCTCCCCACACGGCCGCTCACAATGCCTCGGTGGACAT GTGCGAGCTCAAAAGGGACCTCCAGCTGCTCAGCCAGTTCCTGAAGCATCCCCAGAAGGCCTCAAGGAGGCCCT CGGCTGCCCCGCCAGCCAGCAGTTGCAGAGCCTGGAGTCGAAACTGACCTCTGTGAGATTCATGGGGGACATG GTGTCCTTCGAGGACGGCCGGATCAACGCCACGGTGTGGAAGCTCCAGCCCACAGCCGGCCTCCAGGACCTGCA CATCCACTCCCGGCAGGAGGAGGAGCAGAGCGAGATCATGGAGTACTCGGTGCTGCCTCCGAACACTCTTCC AGAGGACGAAAGGCCGGAGCGGGAGCTGAGAAGACTCCTCCTGGTGGACTTCAGCAGCCAAGCCCTGTTC CAGGACAAGAATTCCAGCCAAGTCCTGGGTGAGAAGGTCTTGGGGGATTGTGGTACAGAACACCAAAGTAGCCAA CCTCACGGAGCCCGTGGTGCTCACTTTCCAGCACCAGCTACAGCCGAAGAATGTGACTCTGCAATGTGTTCT GGGTT GAAGACCCCACATT GAGCAGCCC GGGGCATT GGAGCAGT GCT GGGT GT GAGACCGT CAGGAGAGAAACC CAAACATCCTGCTTCTGCAACCACTTGACCTACTTTGCAGTGCTGATGGTCTCCTCGGTGGAGGTGGACGCCGT CCGCCTACCTCTGCTCCAGGGTGCCCCTGCCGTGCAGGAGAAACCTCGGGACTACACCATCAAGGTGCACATG AACCTGCTGCTGGCCGTCTTCCTGCTGGACACGACCTTCCTGCTCAGCGAGCCGGTGGCCCTGACAGGCTCTGA GGCTGGCTGCCGAGCCAGTGCCATCTTCCTGCACTTCTCCTGCTCACCTGCCTTTCCTGGATGGGCCTCGAGG ATGGGCTGGGGCTTCCCCATCTTTCTGGTGACGCTGGTGGCCCTGGTGGATGTGGACAACTATGGCCCCATCAT ACATCACCAACCTGGGCCTCTTCAGCCTGGTGTTTCTGTTCAACATGGCCATGCTAGCCACCATGGTGGTGCAG ATCCTGCGGCTGCGCCCCACACCCAAAAGTGGTCACATGTGCTGACACTGCTGGGCCTCAGCCTGGTCCTTGG CCTGCCCTGGGCCTTGATCTTCTTCTTCTTCTTGCTTCTGGCACCTTCCAGCTTGTCGTCCTCTACCTTTTCAGCA TCATCACCTCCTTCCAAGGCTTCCTCATCTTCATCTGGTACTGGTCCATGCGGCTGCAGGCCCGGGGTGGCCCC TCCCCTCTGAAGAGCAACTCAGACAGCGCCAGGCTCCCCATCAGCTCGGGCAGCACCTCGTCCAGCCGCATCTA @GCCTCCAGCCCACCTGCCCATGTGATGAAGCAGAGATGCGGCCTCGTCGCACACTGCCTGTGGCCCCCGAGCC AGGCCCAGCCCAGGCCAGTCAGCCGCAGACTTTGGAAAGCCCAACGACCATGGAGAGATGGGCCGTTGCCATG TCAGAAGTGCGCCGCCATGCTGCCTAGGGTACTGTCCCCACATCTGTCCCAACCCAGCTGGAGGCCTGGTCTCT CCTTACAACCCCTGGGCCCAGCCCTCATTGCTGGGGGCCAGGCCTTGGATCTTGAGGGTCTGGCACATCCTTAA CATCCTCTGTCATTTTAACCTCAGGTGGCACCCAGGGCGAATGGGGCCCAGGGCAGACCTTCAGGGCCAGAGCC CTCAGCCCCCAGTCCTCCCTCCATCTTCCCTGGGGTTCTCCTCCTCCCAGGGCCTCCTTGCTCCTTCGTTC ACAGCTGGGGGTCCCCGATTCCAATGCTGTTTTTTGGGGAGTGGTTTCCAGGAGCTGCCTGGTGTCTGCTGTAA ATGTTTGTCTACTGCACAAGCCTCGGCCTGCCCCTGAGCCAGGCTCGGTACCGATGCGTGGGCTGGGCTAGGTC CCT CTGT CCAT CTGGGCCTTTGTATGAGCTGCATTGCCCTTGCTCACCCTGACCAAGCACACGCCTCAGAGGGG CCCTCAGCCTCTCCTGAAGCCCTCTTGTGGCAAGAACTGTGGACCATGCCAGTCCCGTCTGGTTTCCATCCCAC CACTCCAAGGACTGACCTCCTCTGGTGACACTGGCCTAGAGCCTGACACTCTCCTAAGAGGTTCTCTC CTGGAAGACTTCCTGCAGGAGTCAGCGTTCAATCTTGACCTTGAAGATGGGAAGGATGTTCTTTTTACGTACCA ATTCTTTTGTCTTTTGATATTAAAAAGAAGTACATGTTCATTGTAGAGAATTTGGAAACTGTAGAAGAATCA

Page 249 of 359

136/246

FIGURE 134

MTPOSLLQTTLFLLSLLFLVQGABGRCHREDFFFCSQRNQTHRSSLHYKPTPDLRISIENSE
EALTVHAPFPAAHPARRSFDDPRGLYHFCLYWNRHAGRIHLLYGKRDFLLSHKASSLLCFQH
QEESLAQGPPLLATSVTSWWSPQNISLPSAASFTFSFHSPPHTAAHNASVDMCELKRDLQLL
SQFLKHPQKASRRPSAAPASQOLQSLESKLTSVRFMGDMVSFEEDRINATTWKLQPTAGLQD
HHHSRQEEEQSEIMEYSVLLPRTLFQFTKGRSGEAEKKLLLVDFSSQALFQDKNSSQULGE
KULGIVVQNTKVANLTEPVULTFGHQLQPKNVTLQCVFFWEDPTLSSFGHWSSAGCSTVRRE
TQTSCFCNBLTYFAVLMYSSVEVDAVHKHYLSLLSVYGCVVSALACLVTIAAVLCSRVPLPC
RRKPRDYTIKVHMNLLLAVFLLDTSFLLSEPVALTGSEAGCRASAIFLHFSLLTCLSWMGLE
GYNLTRLVVEVFGTYVPGYLKLSAMGWEFPIFLVTLVALVDVDNYGPILAVHRTPEGVIY
PSKOWLTRSUVSYITNLGLFSLVFLFMMAMLATMVVQLIKLRPHTQKWSHVLTLLGLSLVLG
LPMALIFFSFASGTTQLVVLYLFSIITSFQGFLIFWYWSMRLQARGGPSPLKSNSDSARLP
ISSGSTSSSRI

Important features:

WCG268268 [Re://E/W/06266286 opc]

Signal peptide: amino acids 1-25

Putative transmembrane domains:

amino acids 382-398, 402-420, 445-468, 473-491, 519-537, 568-590 and 634-657

Microbodies C-terminal targeting signal.

amino acids 691-693

cAMP- and cGMP-dependent protein kinase phosphorylation sites. amino acids 198-201 and 370-373

N-glycosylation sites.

amino acids 39-42, 148-151, 171-174, 234-237, 303-306, 324-327 and 341-344

G-protein coupled receptors family 2 proteins amino acids 475-504

Page 250 of 359

PCT/US01/21066

WO0268268 [Be://E-W/00206286 opc]

WO 02/08288

137/246

FIGURE 135

GCCTAGCCAGGCCAAGAATGCAATTGCCCCGGTGGTGGGAGCTGGGAGACCCCTGTGCTTGGACGGGACAGGGTCGG CTCCGATCGGAATGTATACCCATCAGCAGGTGTCCTCTTTGTTCATGTTTTGGAAAGAGAATATTTTAAGGGGG AATTTCCACCTTACCCAAAACCTGGCGAGATTAGTAATGATCCCATAACATTTAATACAAATTTAATGGGTTAC CCAGACCGACCTGGATGGCTTCGATATATCCAAAGGACACCATATAGTGATGGAGTCCTATATGGGTCCCCAAC AGCTGAAAATGTGGGGAAGCCAACAATCATTGAGATAACTGCCTACAACAGGCGCACCTTTGAGACTGCAAGGC ATAATTTGATAATTAATATGTCTGCAGAAGACTTCCCGTTGCCATATCAAGCAGAATTCTTCATTAAGAAT ATGAATGTAGAAGAAATGTTGGCCAGTGAGGTTCTTGGAGACTTTCTTGGCGCAGTGAAAAATGTGTGGCAGCC AGAGCGCCTGAACGCCATAAACATCACATCGGCCCTAGACAGGGGTGGCAGGGTGCCACTTCCCATTAATGACC ${\tt TGAAGGAGGCGTTTATGTCATGGTTGGTGCAGATGTCCCGTTTTCTTGTTTACGAGAAGTTGAAAATCCA}$ CAGAAT CAATT GAGAT GTAGT CAAGAAAT GGAGCCT GTAATAACAT GT GATAAAAAATTT CGTACT CAATTT TA CATTGACTGGTGCAAAATTTCATTGGTTGATAAAACAAAGCAAGTGTCCACCTATCAGGAAGTGATTCGTGGAG AGGGGATTTTACCTGATGGTGGAGAATACAAACCCCCTTCTGATTCTTTGAAAAGCAGAGACTATTACACGGAT TTCCTAATTACACTGGCTGTGCCCTCGGCAGTGGCACTGGTCCTTTTTCTAATACTTGCTTATATCATGTGCTG CCGACGGGAAGGCCTGGAAAAGAGAAACATCCAAACACCAGACATCCAACTGGTCCATCACAGTGCTATTCAGA AATCTACCAAGGAGCTTCGAGACATGTCCAAGAATAGAGAGATAGCATGGCCCCTGTCAACGCTTCCTGTGTTC CACCCTGTGACTGGGGAAATCATACCTCCTTTACACACAGACAACTATGATAGCACAAACATGCCATTGATGCA AACGCAGCAGAACTTGCCACATCAGACTCAGATTCCCCAACAGCAGACTACAGGTAAATGGTATCCC<u>TGA</u>AGAA AGAAAACTGACTGAAGCAATGAATTTATAATCAGACAATATAGCAGTTACATCACATTTCTTTTCTCTTCCAAT AATGCATGAGCTTTTCTGGCATATGTTATGCATGTTGGCAGTATTAAGTGTATACCAAATAATACAACATAACT TTCATTTTACTAATGTATTTTTTTGTACTTAAAGCATTTTTGACAATTTGTAAAACATTGATGACTTTATATTT

Page 251 of 359

138/246

FIGURE 136

MOLPRWWELGOPCAWTGGRORTERSPATTGTPLITYYSIESKYHSDRWYYPSAGVLYVHULEREYFKGEFPPY
FKRGEISNDFITNTHLIKGYPDROKURYIGDRTYSDGUIKSFFTARWKKFTJEITATMINETTETARHILLII
NIMSABDFFLPYQABFFTKNNNYEMIASBVIKGFTSGAVKNWOPERIANINITSALDRGGRVPLDFINNLKEGV
YUWWGADVPPSSCLREVENBFONGLGCSGEBEVTTCHKEFFTYTTTSKTHANINITSALDRGGRVPLDFINNLKEGV
DGGBYKPPSDSLKSRNYTTDFLTTAUPSAVALUTHILIMCGRRGVEKNNOCTPDIQUVHSAIQKSTKE
LRDMSKNREIAFMPLSTLPVPHYTGEIIPPLHTDTNDSTNMPLMOTOONLPHOOTOPOOTTGKNYP

signal sequence: Amino acids 1-46

WO0268268 [Be://E-W/00206286 opc]

transmembrane domain: Amino acids 319-338

N-glycosylation site: Amino acids 200-204

cAMP- and cGMP-dependent protein kinase phosphorylation site: Amino acids 23--27

Tyrosine kinase phosphorylation site: Amino acids 43-52

N-myristoylation sites:

Amino acids 17-23;112-118;116-122;

185-191

Page 252 of 359

WC6268368 [Her//E/W/06266286 opc]

WO 02/08288 PCT/US01/21066

139/246

FIGURE 137

CAGAAGAGGGGGCTAGCTGTCTCTGCGGACCAGGGAGACCCCGGGCCCCCCGGTGT GAGTGTGTGGAACAGGACCCGGGACAGAGGAACCATGGCTCCGCAGAACCTGAGCACCTTTT GCCTGTTGCTGCTATACCTCATCGGGGCGGTGATTGCCGGACGAGATTTCTATAAGATCTTG GGGGTGCCTCGAAGTGCCTCTATAAAGGATATTAAAAAGGCCTATAGGAAACTAGCCCTGCA GCTTCATCCCGACCGGAACCCTGATGATCCACAAGCCCAGGAGAAATTCCAGGATCTGGGTG CTGCTTATGAGGTTCTGTCAGATAGTGAGAAACGGAAACAGTACGATACTTATGGTGAAGAA GGATTAAAAGATGGTCATCAGAGCTCCCATGGAGACATTTTTTCACACTTCTTTGGGGATTT TGGTTTCATGTTTGGAGGAACCCCTCGTCAGCAAGACAGAAATATTCCAAGAGGAAGTGATA TTATTGTAGATCTAGAAGTCACTTTGGAAGAAGTATATGCAGGAAATTTTGTGGAAGTAGTT AGAAACAAACCTGTGGCAAGGCAGGCTCCTGGCAAACGGAAGTGCAATTGTCGGCAAGAGAT GCGGACCACCCAGCTGGGCCCTGGGCGCTTCCAAATGACCCAGGAGGTGGTCTGCGACGAAT GCCCTAATGTCAAACTAGTGAATGAAGAACGAACGCTGGAAGTAGAAATAGAGCCTGGGGTG AGAGACGCATGGAGTACCCCTTTATTGGAGAAGGTGAGCCTCACGTGGATGGGGAGCCTGG TGTACACAAATGTGACAATCTCATTAGTTGAGTCACTGGTTGGCTTTGAGATGGATATTACT CACTTGGATGGTCACAAGGTACATATTTCCCGGGATAAGATCACCAGGCCAGGAGCGAAGCT ATGGAAGAAAGGGGAAGGGCTCCCCAACTTTGACAACAACAATATCAAGGGCTCTTTGATAA TCACTTTTGATGTGGATTTTCCAAAAGAACAGTTAACAGAGGAAGCGAGAGAAGGTATCAAA CAGCTACTGAAACAAGGGTCAGTGCAGAAGGTATACAATGGACTGCAAGGATAT**TGA**GAGTG TCATCATGAAATGAATAAGAGGGCTTAAGAATTTGTCCATTTGCATTCGGAAAAGAATGACC AGCAAAAGGTTTACTAATACCTCTCCCTTTGGGGATTTAATGTCTGGTGCTGCCGCCTGAGT TTCAAGAATTAAAGCTGCAAGAGGACTCCAGGAGCAAAAGAAACACAATATAGAGGGTTGGA GTTGTTAGCAATTTCATTCAAAATGCCAACTGGAGAAGTCTGTTTTTAAATACATTTTGTTG TTATTTTTA

Page 253 of 359

WO 02/08288 PCT/US01/21066

140/246

FIGURE 138

MAPQMLSTPCLLLLYLIGAVIAGROPYKILGVPRASIKDIKKAYRKLALOLHPORNPODPQAGEKPODLGAAY
EVISDSEKRKQYDTYGBEGLKDGHQSSHGDIFSHFFGDFGMFGGTPRQDRNIPRGSDITVDLEVTLEEVVAG
NEVEVVRNKPVARQA-GKRKONCRGEMRITQLGFGKFQMTGEVVCDSCPNYKLNNEERTLEVEIEFGVRGMEY
PFIGEGEPHVDGEFGDLRFRIKVVKHPIFERRGDDLYTHVTISIWSLVGFEMDITHLDGHKVHISRDKITRFG
AKJMKKGGGLHFPNNNNIXGSLITFPVDPFREQDEERARGIKGLLKQGSVQKYNNGLQGY

Important features: Signal peptide: amino acids 1-22

WC0268268 [Be://E-W/00206286 opc]

Cell attachment sequence. amino acids 254-257

Nt-dnaJ domain signature. amino acids 67-87

Homologous region to Nt-dnaJ domain proteins. amino acids 26-58

N-glycosylation site. amino acids 5-9, 261-265

Tyrosine kinase phosphorylation site. amino acids 253-260

N-myristoylation site. amino acids 18-24, 31-37, 93-99, 215-221

Amidation site. amino acids 164-168

WO0268268 [Be://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 254 of 359

141/246

FIGURE 139

WCc008088 (He ///E NVOV208288 opt.) Page 255 of 554

WO 02/08288 PCT/US01/21066

142/246

FIGURE 140

</usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA56405
<subunit 1 of 1, 125 aa, 1 stop
<mm: 13115, pr: 5.90, NX (S/T): 1
MRGTRLALLALVLAACGELAPALRCYVCPEPTGVSDCVTLATCTTNETMCKTTLYSREIVYP
FQQDSTVTKSCASKCKPSDUDGIGQTLPVSCCNTELCNVDGAPALNSLHGGALTLLPLLSLRL</pre>

Important features: Signal peptide: amino acids 1-17

N-glycosylation site. amino acids 46-49

Page 256 of 359

WCG268268 [IB#7/E-AV-06206236 opc.]

WO 02/08288 PCT/US01/21066

143/246

FIGURE 141

GGCGCCGCTAGGCCCGGAGGCCGGCCGGCCGGCTGCGAGCGCCTGCCCCATGCGCCGC CGCCTCTCCGCACGATGTTCCCCTCGCGGAGGAAAGCGGCCAGCTGCCCTGGGAGGACGGC AGGTCCGGGTTGCTCCCGGCGGCCTCCCTCGGAAGTGTTCCGTCTTCCACCTGTTCGTGGC CTGCCTCTCGCTGGGCTTCTTCTCCCTACTCTGGCTGCAGCTCAGCTGCTCTGGGGACGTGG CCGCCCCTGAGCACTGGGAAGAAGACGCATCCTGGGGCCCCCACCGCCTGGCAGTGCTGGT GCCCTTCCGCGAACGCTTCGAGGAGCTCCTGGTCTTCGTGCCCCACATGCGCCGCTTCCTGA GCAGGAAGAAGATCCGGCACCACATCTACGTGCTCAACCAGGTGGACCACTTCAGGTTCAAC CGGGCAGCGCTCATCAACGTGGGCTTCCTGGAGAGCAGCAACAGCACGGACTACATTGCCAT GCACGACGTTGACCTGCTCCTCTCAACGAGGAGCTGGACTATGGCTTTCCTGAGGCTGGGC CCTTCCACGTGGCCTCCCCGGAGCTCCACCCTCTCTACCACTACAAGACCTATGTCGGCGGC ATCCTGCTGCTCCAAGCAGCACTACCGGCTGTGCAATGGGATGTCCAACCGCTTCTGGGG CTGGGGCCGCGAGGACGACGAGTTCTACCGGCGCATTAAGGGAGCTGGGCTCCAGCTTTTCC GCCCTCGGGAATCACAACTGGGTACAAGACATTTCGCCACCTGCATGACCCAGCCTGGCGG CCTGCACTGTCCTCAACATCATGTTGGACTGTGACAAGACCGCCACACCCTGGTGCACATTC AGCTGAGCTGGATGGACAGTGAGGAAGCCTGTACCTACAGGCCATATTGCTCAGGCTCAGGA CAAGGCCTCAGGTCGTGGGCCCAGCTCTGACAGGATGTGGAGTGGCCAGGACCAAGACAGCA AGCTACGCAATTGCAGCCACCCGGCCGCCAAGGCAGGCTTGGGCTGGGCCAGGACACGTGGG GGACCCCCCTGCCTTCCTGCTCACCCTACTCTGACCTCCTTCACGTGCCCAGGCCTGTGGG TAGTGGGGAGGCTGAACAGGACAACCTCTCATCACCCTACTCTGACCTCCTTCACGTGCCC

Page 257 of 359

144/246

FIGURE 142

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA56531

><subunit 1 of 1, 327 aa, 1 stop

><MW: 37406, pI: 9.30, NX(S/T): 1

MFPSRRKAAQLPWEDGRSGLLSGGLPRKCSVFHLFVACLSLGFFSLLWLQLSCSGDVARAVR GQCQETSGPPRACPPEPPPEHWEEDASWGPHRLAVLVPFRERFEELLVPYPHMRRFLSRKKI RHHIYYLNQVDHFRFNRAALINVGFLESSNSTDYIAMHDVDLLPLNEELDYGFPEAGFFHVA SPELHPLYHYKTYVGGILLLSKQHYRLCNGMSNRFWGWGREDDEFYRRIKGAGLQLFRPSGI TTGYKTFRHLHDPAWRKKDQKRIAAQKQEQFKVDREGGLNTVKYHVASRTALSVGGAPCTVL NIMLDCDKTAATFWCTFS

Signal peptide:

WCG208268 [Re://E/W/00206286 opc]

amino acids 1-42

Transmembrane domain:

amino acids 29-49 (type II)

N-glycosylation site. amino acids 154-158

cAMP- and cGMP-dependent protein kinase phosphorylation site. amino acids 27-31

Tyrosine kinase phosphorylation site.

amino acids 226-233

N-myristoylation site.

amino acids 19-25, 65-71, 247-253, 285-291, 303-309, 304-310

Page 258 of 359

WC0268268 [Be://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

145/246

FIGURE 143

CTTTGTCCGAACAGCTCCCCTCTGCCAGCTTCTGTAGATAAGGGTTAAAAACTAATATTTATATGACAGAAGAA AAAGATGTCATTCCGTAAAGTAAACATCATCATCTTGGTCCTGGCTGTTGCTCTTCTTACTGGTTTTGCACC ATAACTTCCTCAGCTTGAGCAGTTTGTTAAGGAATGAGGTTACAGGATTCAGGAATTGTAGGGCCTCAACCTATA GACTTTGTCCCAAATGCTCTCCGACATGCAGTAGATGGGAGACAAGAGGAGATTCCTGTGGTCATCGCTGCATC TGAAGACAGGCTTGGGGGGGCCATTGCAGCTATAAACAGCATTCAGCACACACCTCGCTCCAATGTGATTTTCT ACATTGTTACTCTCAACAATACAGCAGACCATCTCCGGTCCTGGCTCAACAGTGATTCCCTGAAAAGCATCAGA GAAACCTTTAACCTTTGCAAGGTTCTACTTGCCAATTCTGGTTCCCAGCGCAAAGAAGGCCATATACATGGATG ATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTACAATACAGCACTGAAGCCAGGACATGCAGCTGCATTT TCAGAAGATTGTGATTCAGCCTCTACTAAAGTTGTCATCCGTGGAGCAGGAAACCAGTACAATTACATTGGCTA TCTTGACTATAAAAAGGAAAGAATTCGTAAGCTTTCCATGAAAGCCAGCACTTGCTCATTTAATCCTGGAGTTT GAAGAGGGACTGTATAGCAGAACCCTGGCTGGTAGCATCACACCCCTCCTCTTGCTTATCGTATTTTATCAACA GCACTCTACCATCGATCCTATGTGGAATGTCCGCCACCTTGGTTCCAGTGCTGGAAAACGATATTCACCTCAGT TTGTAAAGGCTGCCAAGTTACTCCATTGGAATGGACATTTGAAGCCATGGGGAAGGACTGCTTCATATACTGAT GTTT GGGAAAAAT GGTATATTCCAGACCCAACAGGCAAATTCAACCTAATCCGAAGATATACCGAGATCTCAAA TAACAGTTGCTAGGCTTCAATGCCTATCGGTAGCAAGCCATGGAAAAAGATGTGTCAGCTAGGTAAAGATGACA A A CTGCCCTGTCTGGCAGTCAGCTTCCCAGACAGACTATAGACTATAAATATGTCTCCATCTGCCTTACCAAGT

WC0268268 [Be://E-W/06206236 opc]

WO 02/08288 PCT/US01/21066

Page 259 of 359

146/246

FIGURE 144

MSFRKVNIIILVLAVALFILVLHHNFLSLSSLIRNEVTDSGIVGPOPIDFVPNALRHAVDCR QEEIPVVIAASEDRLGGAIAAINSIQHNTRSNVIFYIVTLNNTADHLRSWINSDSLKSIRYK IVNFDPKLLEGKVKEDPDQGESMKPLTFARFYLPILVPSAKKAIYMDDDVIVQGDILALVNT ALKPGHAAAFSEDCDSASTKVVIRGAGNQYNYIGYLDYKKERIRKLSMKASTCSFNPGVFVA NITEWKRQNITNQLEKWMKLNVEEGLYSRTLAGSITTPPLLIVFYQQHSTIDPWMNVRHLGS SAGKRYSPQFVKAAKLLHWNGHLKPWGRTASYTDVWEKWYIPDPTGKFNLIRKYTEISNIK

Page 280 of 359

147/246

WCG208268 [He://E./W/00206286 opc]

FIGURE 145

Page 281 of 359

WCG208268 [He://E-/W/00206286 opc]

148/246

FIGURE 146

 $\label{eq:mkipvlpavvllsllvlhsa} $$ MKIPVLPAVVLLSLLVLHSAQGATLGGPEEESTIENYASRPEAFNTPFLNIDKLRSAFKADE FLNWHALFESIKRKLPFLNWDAFPKLKGLRSATPDAO $$$

149/246

FIGURE 147

 WCG268268 [IRe://E./WO6206286 opc]

WO 02/08288

PCT/US01/21066

Page 283 of 359

150/246

FIGURE 148

MKFTI VEAGLLGV FLAPALANYN I NVNDDNNNAGSGQQSVSVNNEHNVANVDNNNGWDSWNS IWDYGNGFAATTLF DKKTC I KHNINKEVMPSI OSLDALVKEKKLQGKGPGGPP FKGLMYSVN PNKYDDLSKFGKNI I ANMCI OF I TYMAGEMOGASLFFYSGTCYTTSVLWI VDIS FCGDT VEN

Signal Peptide: amino acids 1-20

N-myristoylation Sites:

amino acids 67-72, 118-123, 163-168

Flavodoxin protein homology: amino acids 156-174

Page 284 of 359

151/246

WO0268268 [He://E-W/00206286 opc]

FIGURE 149

ATGGGGCTCCCTGGGCTGTTCTGCTTGGCCGTGCTGCCAGCAGCTTCTCCAAGGCACG GGAGGAAGAAATTACCCCTGTGGTCTCCATTGCCTACAAAGTCCTGGAAGTTTTCCCCAAAG GCCGCTGGGTGCTCATAACCTGCTGTGCACCCCAGCCACCGCCCATCACCTATTCCCTC TGTGGAACCAAGAACATCAAGGTGGCCAAGAAGGTGGTGAAGACCCACGAGCCGGCCTCCTT CAACCTCAACGTCACACTCAAGTCCAGTCCAGACCTGCTCACCTACTTCTGCCGGGCGTCCT CCACCTCAGGTGCCCATGTGGACAGTGCCAGGCTACAGATGCACTGGGAGCTGTGGTCCAAG CCAGTGTCTGAGCTGCGGGCCAACTTCACTCTGCAGGACAGAGGGGCAGGCCCCAGGGTGGA GATGATCTGCCAGGCGTCCTCGGGCAGCCCACCTATCACCAACAGCCTGATCGGGAAGGATG AGCCAGACATCGGACTGGTTCTGGTGCCAGGCTGCAAACAACGCCAATGTCCAGCACAGCGC CCTCACAGTGGTGCCCCCAGGTGGTGACCAGAAGATGGAGGACTGGCAGGGTCCCCTGGAGA GCCCCATCCTTGCCTTGCCGCTCTACAGGAGCACCCGCCGTCTGAGTGAAGAGGAGTTTGGG GGGTTCAGGATAGGGAATGGGGAGGTCAGAGGACGCAAAGCAGCAGCCATGTAGAATGAACC GTCCAGAGAGCCAAGCACGCAGAGGACTGCAGGCCATCAGCGTGCACTGTTCGTATTTGGA

WO 02/08288

PCT/US01/21066

152/246

FIGURE 150

MGLPGLFCLAVLAASSFSKAREBEITPVVSIAVKVLEVPFKGRWVLITCCAPQPPPPITYSL CGTKNIKVAKKVVKTHEPASFNLNVTLKSSPDLLTYFCRASSTSGAHVDSARLQMHWELMSK PVSELRANFTLQDRCAGFRVEMICQASSGSPPITNSLICKDGOVHLQQRPCHRQPANFSFLP SQTSDWFWCQAANNANVQHSALTVVPPGGDQKMEDWQGPLESPILALPLYRSTRRLSEEEFG GFRIGNGEVRGKRAAM

Signal Peptide: amino acids 1-18

N-glycosylation Sites: amino acids 86-89, 132-135, 181-184

Page 286 of 359

153/246

WCG268268 [IB#1//E-AVO6206286 opc.]

FIGURE 151

 MCG008068 (like W.E. An Oxfoesse opt)

WO 02/08288 PCT/US01/21066

154/246

FIGURE 152

 $\verb|MSRSSKVVLiglsvlltaatvagvhvkqqwdqqrlrdgvirdierqirkkenirllgeqiilt eqleaerekmllakgsqks|$

WC6268368 (Her//E/W/06266286 opc)

WO 02/08288 PCT/US01/21066

Page 288 of 359

155/246

FIGURE 153

AATGTGAGAGGGGCTGATGGAAGCTGATAGGCAGGACTGGAGTGTTAGCACCAGTACTGGAT GTGACAGCAGCAGGAGGAGCACTTAGCAGCTTATTCAGTGTCCGATTCTGATTCCGGCAAGG ATCCAAGCATGGAATGCTGCCGTCGGGCAACTCCTGGCACACTGCTCCTCTTTCTGGCTTTC CTGCTCCTGAGTTCCAGGACCGCACGCTCCGAGGAGGACCGGGCCTATGGGATGCCTG GCCTGAGCAGCAGGAGCTGTGAAGGAAGAAATATCCGATACAGAACATGCAGTAATGTGGAC TGCCCACCAGAAGCAGGTGATTTCCGAGCTCAGCAATGCTCAGCTCATAATGATGTCAAGCA CCATGGCCAGTTTTATGAATGGCTTCCTGTGTCTAATGACCCTGACAACCCATGTTCACTCA AGTGCCAAGCCAAAGGAACAACCCTGGTTGTTGAACTAGCACCTAAGGTCTTAGATGGTACG CGTTGCTATACAGAATCTTTGGATATGTGCATCAGTGGTTTATGCCAAATTGTTGGCTGCGA TCACCAGCTGGGAAGCACCGTCAAGGAAGATAACTGTGGGGTCTGCAACGGAGATGGGTCCA CCTGCCGGCTGGTCCGAGGGCAGTATAAATCCCAGCTCTCCGCAACCAAATCGGATGATACT GTGGTTGCACTTCCCTATGGAAGTAGACATATTCGCCTTGTCTTAAAAGGTCCTGATCACTT ATATCTGGAAACCAAAACCCTCCAGGGGACTAAAGGTGAAAACAGTCTCAGCTCCACAGGAA CTTTCCTTGTGGACAATTCTAGTGTGGACTTCCAGAAATTTCCAGACAAAGAGATACTGAGA ATGGCTGGACCACTCACAGCAGATTTCATTGTCAAGATTCGTAACTCGGGCTCCGCTGACAG CTTGCTCAGCAACCTGTGGAGGAGGTTATCAGCTGACATCGGCTGAGTGCTACGATCTGAGG AGCAACCGTGTGGTTGCTGACCAATACTGTCACTATTACCCAGAGAACATCAAACCCAAACC CAAGCTTCAGGAGTGCAACTTGGATCCTTGTCCAGCCAGTGACGGATACAAGCAGATCATGC CTTATGACCTCTACCATCCCCTTCCTCGGTGGGAGGCCACCCCATGGACCGCGTGCTCCTCC TCGTGTGGGGGGGCATCCAGAGCCGGGCAGTTTCCTGTGTGGAGGAGGACATCCAGGGGCA TGTCACTTCAGTGGAAGAGTGGAAATGCATGTACACCCCTAAGATGCCCATCGCGCAGCCCT GCAACATTTTTGACTGCCCTAAATGGCTGGCACAGGAGTGGTCTCCGTGCACAGTGACATGT GGCCAGGGCCTCAGATACCGTGTGGTCCTCTGCATCGACCATCGAGGAATGCACACAGGAGG CTGTAGCCCAAAAACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACTCCCTGCTATA AACCCAAAGAGAAACTTCCAGTCGAGGCCAAGTTGCCATGGTTCAAACAAGCTCAAGAGCTA GAAGAAGGAGCTGCTGTCAGAGGAGCCCTCGTAAGTTGTAAAAGCACAGACTGTTCTATA TTTGAAACTGTTTTGTTTAAAGAAAGCAGTGTCTCACTGGTTGTAGCTTTCATGGGTTCTGA AAAAAAAA

Page 289 of 359

WO 02/08288 PCT/US01/21066

156/246

FIGURE 154

</user/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA58847
<subunit 1 of 1, 525 aa, 1 stop
<mm: 58416, pi: 6.62, NX (S/T): 1
MECCRRATEGTLILFLAFLLLSSKTARSEEDRIGLWDAWGPWSECSRTCGGGASYSLRRCLS
KSCEGRNIRYRTCSNVDCPPEAGDFRAQQCSAHNDVKHHGQFYEWLPVSNDPDNPCSLKCQ
AKGTTLVVELAFKVLDGTRCYTESLDWCISGLCQIVGCDHQLGSTVKEDNGGVCNGDGSTCR
LVRGQYKSQLSATKSDDTVVALPYGSRHIRLVLKGPDHLYLETKTLQGTKGENSLSSTGFFL
VONSSVDFGVFPDKEILFMAGPFTAPDFIVKIRNGSADSTVOFIFYQPIIRWRETDFFPCS
ATCGGGYQLTSAECYDLRSNRVVADQYCHYYPENIKPKPKLQECNLDPCPASDGYKQIMPYD
LYHPLPRWBATFWTACSSSCGGGIQSRAVSCVEEDIQGHVTSVEEWKCWYTPKWFIAQPCNI
FDCPKKLAGDWSPCTVTCGOGLKYRVVLICIDHRGWHTGGCSFKTWPHIKECIUPTFCYKPK</pre>

Important features:
Signal peptide:
amino acids 1-25

EKLPVEAKLPWFKOAOELEEGAAVSEEPS

WC0268268 [Be://E-W/00206286 opc]

N-glycosylation site. amino acids 251-254

Thrombospondin 1 amino acids 385-399

von Willebrand factor type C domain proteins amino acids 385-399, 445-459 and 42-56

WCG268268 (IB#7/E-AVO6206286 opc.)

WO 02/08288 PCT/US01/21066

Page 270 of 359

157/246

FIGURE 155

CTCTGCCTGGGCAGTGGGGAGGCTGGCCCCCTGCAGAGCGGAGAGGGAAAGCACTGGGACAAATATTGGGGAGGC CCTTGGACATGGCCTGGGAGACGCCCTGAGCGAAGGGGTGGGAAAGGCCATTGGCAAAGAGGCCGGAGGGGCAG GGCTTTGGCGCAGCAGATGCTTTGGGCAACAGGGTCGGGGAAGCAGCCCATGCTCTGGGAAACACTGGGCACGA GATTGGCAGACAGCAGAAGATGTCATTCGACACGGAGCAGATGCTGTCCGCGGCTCCTGGCAGGGGGTGCCTG GCCACAGTGGTGCTTGGGAAACTTCTGGAGGCCATGGCATCTTTGGCTCTCAAGGTGGCCTTGGAGGCCAGGGC GARTCCTCAGGGAGCTCCCTGGGGTCAAGGAGGCCAATGGAGGGCCACCAAACTTTGGGACCAACACTCAGGGAG CTGTGGCCCAGCCTGGCTATGGTTCAGTGAGAGCCAGCAACCAGAATGAAGGGTGCACGAATCCCCCACCATCT GGCTCAGGTGGAGGCTCCAGCAACTCTGGGGGAGGCAGCGGCTCACAGTCGGGCAGCAGTGGCAGCAGCAA ${\tt GCAGTGGCGGCAGCAGTGGCAGCAGTGGCAACAGTGGTGGCAGCAGGGGGAGGGGGCAGTGAGTCCTCC}$ TGGGGATCCACCGGCTCCTCCTCCGGCAACCACGGTGGGAGCGGCGGAGGAAATGGACATAAACCCGGGTG TGAAAAGCCAGGGAATGAAGCCCGCGGGAGCGGGGAATCTGGGATTCAGGGCTTCAGAGGACAGGGAGTTTCCA GCAACATGAGGGAAATAAGCAAAGAGGGCAATCGCCTCCTTGGAGGCTCTGGAGACAATTATCGGGGGCAAGGG GTTTAACTTTGACACTTTCTGGAAGAATTTTAAATCCAAGCTGGGTTTCATCAACTGGGATGCCATAAACAAGG ACCAGAGAAGCTCTCGCATCCCGTGACCTCCAGACAAGGAGCCACCAGATTGGATGGGAGCCCCCACACTCCCT CCTTAAAACACCACCCTCTCATCACTAATCTCAGCCCTTGCCCTTGAAATAAACCTTAGCTGCCCCACAAAAA

Page 271 of 359

WO 02/08288 PCT/US01/21066

158/246

FIGURE 156

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA59212

><subunit 1 of 1, 440 aa, 1 stop

><MW: 42208, pI: 6.36, NX(S/T): 1

Signal peptide:

WCG268268 (IB#7/E-AVO6206286 opc.)

amino acids 1-21

N-glycosylation site.

amino acids 265-269

Glycosaminoglycan attachment site.

amino acids 235-239, 237-241, 244-248, 255-259, 324-328, 388-392

Casein kinase II phosphorylation site.

amino acids 26-30, 109-113, 259-263, 300-304, 304-308

N-myristoylation site.

amino acids 17-23, 32-38, 42-48, 50-56, 60-66, 61-67, 64-70, 74-80, 90-96, 96-102, 130-136, 140-146, 149-155, 152-158, 155-161, 159-165, 163-169, 178-184, 190-196, 194-200, 199-205, 218-224, 236-242, 238-244, 239-245, 240-246, 245-251, 246-252, 249-252, 253-259, 256-262, 266-272, 270-276, 271-277, 275-281, 279-285, 283-289, 284-290, 287-293, 288-294, 291-297, 292-296, 295-301, 298-304, 305-311, 311-317, 315-321, 319-325, 322-328, 333-339, 387-393, 389-395, 395-401

Cell attachment sequence.

amino acids 301-304

159/246

FIGURE 157

CCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCCACGCGTCCGC TCTGCAGCTGCCCGGGGCGCGAATGGCAGGCTGTTTCCGCGGAGTAAAAGGTGGCCCGGTCAGTGGTCGT CAATGACGGACATTAACCAGACTGTCAGATCCTGGGGAGTCGCGAGCCCCGAGTTTTGGAGTTTTTTCCCCC LACOTTIC CONTINUE AND A CONTINUE AND GACCGAGCGCTTCCAATGGACATTCTCCAGTCTCTCTGGAAAGATTCTCCGCTAATGGATTTCCTGCTCCTCGGT CTCTGTCTATACTGGCTGCTGAGGAGGCCCTCGGGGGTGGTCTTGTGTCTGCTGGGGGCCTGCTTTCAGATGCT GCCGGCCAGTTCACGGGGTTAATGCAGCTCACGTGGCTCTATCTGGATCACAATCACATCTGCTCCGTGCAGGG GGACGCCTTTCAGAAACTGCGCCGAGTTAAGGAACTCACGCTGAGTTCCAACCAGATCACCCAACTGCCCAACA CCACCTTCCGGCCCATGCCCAACCTGCGCAGCCTGGACCTCTCCTACAACAAGCTGCAGGCGCTCGCGCCCGACCTCTCCACGGGCTGCGCATGCGCATATGCGGGCCAACGCCATCCAGTTTGTGCCCGTGCGCAT CTTCCAGGACTGCCGCAGCCTCAAGTTTCTCGACATCGGATACAATCAGCTCAAGAGTCTGGCGCGCAACTCTT TCGCCGGCTTGTTTAAGCTCACCGAGCTGCACCTCGAGCACAACGACTTGGTCAAGGTGAACTTCGCCCACTTC CCGCGCCTCATCTCCCTGCACTCGCTCTGCCTGCGAGGAACAAGGTGGCCATTGTGGTCAGCTCGCACTGGGTTTGGAACCTGGAGAAAATGGACTTGTCGGGCAACGAGATCGAGTACATGGAGCCCCATGTGTTCGAGACCC TGCCGCACCTGCACTCCCTGCAGCTGCACTCCAACCGCCTCACCTACATTCGAGCCCCGGATCCTCAACTCTTTGG AAGTCCCTGACAAGCATCACCTGGCCGGGAACCTGTGGGATTGCGGGCGCAACCTGTGTGTCCCCTAGCCTCGTG GCTCAGCAACTTCCAGGGGCGCTACGATGGCAACTTGCAGTGCGCAGCCCGGAGTACGCACAGGGCGAGGACG TCCTGGACGCCGTGTACGCCTTCCACCTGTGCGAGGATGGGGCCGAGCCCACCAGCGGCCACCTGCTCTCGGCC GTCACCAACCGCAGTGATCTGGGGCCCCCTGCCAGCTCGGCCACCCCGCTCGCGGACGGCGGGGGAGGGCCAGCA CGACGCCACATTCGAGCCTGCCACCGTGGCTCTTCCAGGCGGCGAGCACGCCGAGAACGCCGTGCAGATCCACA AGCTGGT CACGGGCACCATGGCCCTCATCTTCTCCTTCCTCATCGTGCTCCTGGTGCTCTACGTGTCCTGGAAG TGTTTCCCAGCCAGCCTCAGGCAGCTCAGACAGTGCTTTGTCACGCAGCGCAGGAAGCAAAAGCAGAAACAGAC CATGCATCAGATGGCTGCCATGTCTGCCCAGGAATACTACGTTGATTACAAACCGAACCACATTGAGGGAGCCC TGGTGATCHTCHACGAGTATGGCTTCGTGTACCTCCACCAGCAGCCCCCGGGGGAATCCGAGCTG<u>TGA</u>TTGTCC CAGTGGCTCTCAACCCATCCGCTACCAAATCCGCTGGGCGCCGGGGGGCGCGGGGCACCAGGCTGGGC CTCCTTGTCTGTGTCTGATATGCTCCTTGACTGAAACTTTAAGGGGATCTCCCCAGAGACTTGTAG CTTTATTGTGTCTTAAAAACAAAAGCGAATTAAAACACAACAAAAAACCCCACCCCACAACCTTCAGGACAGTC TTAGCATCAACAACACATTTATGAGTATATGTAAGTAATCAGAGGGGCAAATGCCACTTGTTATTCCTCCCA ATTIMOCHLANDANCANTITALISMINITANIAN TANDANG MENGANG AND ANTONIO THE CONTROL OF THE

Page 273 of 359

WC0268268 [Be://E-W/00206286 opc]

160/246

FIGURE 158

MPFLILGLCLYWILRERSGVVILCLIGACTOMIPAAPSGCPOLCCCSGRILYCEAUNITEAPHNISGLIGISLEY
NSISSLERAGOFFGLMQLIWIYLDINHICSVGODAFOKRREWKLITISSION [170] ENTFTREPREISSUSSYNK
LQALAPDLFFGLRRIJTHIMBANAIQPPVPRIFODCRSIKFLDIGYNGLKSLARNSFRAGIFKITEHHEIRNDLV
KWIFAHFPRIJALBISLIGERSWKVAIVVSSLOWWINLEKMDLSKOHIETWREPWFETVPHLGSLODSNETTYTE
PRIINSKKSLTSITLAGNLWDCGRNVCALASWISNFOGRYDGNIQCASPEYAGGEDVLDAVYAFHLCEDGAEPT
SCHLLSAVINSBOLGPPASSATTLADGGEGORDFOFFPATVAHDGGEBLEANWOJHKVVTGTMALTFSFLIVUV
LVYVSNKCFFASLRQLRQCFVTORKKOKOKOTMHOMAAMSAQEYYVDYKPNHIEGALVIINEYGSCTCHQOPAR
EGEV

Page 274 of 359

WG0268268 [Be://E-W/00206286 epc]

161/246

FIGURE 159

CAGAGAGGAGGCTTTGGGAATTGTCCAGCAGAAACAGAGAAGTCTGAGGTGTGTCAAGACA AAAGATGCTTCAGCTTTGGAAACTTGTTCTCCTGTGCGGCGTGCTCACTGGGACCTCAGAGTCT CTTCTTGACAATCTTGGCAATGACCTAAGCAATGTCGTGGATAAGCTGGAACCTGTTCTTCA CGAGGGACTTGAGACAGTTGACAATACTCTTAAAGGCATCCTTGAGAAACTGAAGGTCGACC TAGGAGTGCTTCAGAAATCCAGTGCTTGGCAACTGGCCAAGCAGAAGGCCCAGGAAGCTGAG AAATTGCTGAACAATGTCATTTCTAAGCTGCTTCCAACTAACACGGACATTTTTGGGTTGAA ACCTGAGCTTCCCTGTCACCGCGAATGTCACTGTGGCCGGGCCCATCATTGGCCAGATTATC AACCTGAAAGCCTCCTTGGACCTCCTGACCGCAGTCACAATTGAAACTGATCCCCAGACACA CCAGCCTGTTGCCGTCCTGGGAGAATGCGCCAGTGACCCAACCAGCATCTCACTTTCCTTGC TGGACAAACACAGCCAAATCATCAACAAGTTCGTGAATAGCGTGATCAACACGCTGAAAAGC ACTGTATCCTCCCTGCTGCAGAAGGAGATATGTCCACTGATCCGCATCTTCATCCACTCCCT GGATGTGAATGTCATTCAGCAGGTCGTCGATAATCCTCAGCACAAAACCCAGCTGCAAACCC TCATCTGAAGAGGACGAATGAGGAGGACCACTGTGGTGCATGCTGATTGGTTCCCAGTGGCT TGCCCCACCCCTTATAGCATCTCCCTCCAGGAAGCTGCTGCCACCACCTAACCAGCGTGAA AGCCTGAGTCCCACAGAAGGACCTTCCCAGATACCCCTTCTCCTCACAGTCAGAACAGCAG CCTCTACACATGTTGTCCTGCCCCTGGCAATAAAGGCCCATTTCTGCACCCTTAA

MC00080188 [ight N.E. VA.Ooxtoessa, doc!

WO 02/08288 PCT/US01/21066

Page 275 of 359

162/246

FIGURE 160

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA59622

><subunit 1 of 1, 249 aa, 1 stop

><MW: 27011, pI: 5.48, NX(S/T): 2

MLQLMKLVLLCGVJTGTTSESLLDNLGNDLSNVVOKLBFVLHEGLETVDNTLKGILEKLKV DLGVLQKSSAWQLAKQKAQEAEKLLNNVISKLLPTNTDIFGLKISNSLILDVKAEFIDDG KGLNLSFFVTANVTVAGFIIGQIINLKASLDLLTAVTIETDFQTHQFVAVLGECASDFTS ISLSLLDKHSQIINKFVNSVINTLKSTVSSLLQKEICPLIRIFIHSLDVNVIQQVVDNPQ HKTQLQTLI

Important features:

Signal peptide:

Amino acids 1-15

N-glycosylation sites:

Amino acids 124-128;132-136

N-myristoylation sites:

Amino acids 12-18;16-22;26-32;101-107;122-128;141-147

Leucine zipper pattern:

Amino acids 44-66

Page 276 of 359

163/246

WC0268268 [Be://E_W/06206286 opc.]

FIGURE 161

CAGCCACAGACGGGTCATGAGCGCGGTATTACTGCTGGCCCTCCTGGGGTTCATCCTCCCAC TGCCAGGAGTGCAGGCGCTGCTCTGCCAGTTTGGGACAGTTCAGCATGTGTGGAAGGTGTCC GACCTACCCCGGCAATGGACCCCTAAGAACACCAGCTGCGACAGCGGCTTGGGGTGCCAGGA CACGTTGATGCTCATTGAGAGCGGACCCCAAGTGAGCCTGGTGCTCCCAAGGGCTGCACGG AGGCCAAGGACCAGGAGCCCCGCGTCACTGAGCACCGGATGGGCCCCGGCCTCTCCCTGATC TTGGGCCCCACAGCCCCAGCAGACCCAGGATCCTTGAGGTGCCCAGTCTGCTTGTCTATGG AAGGCTGTCTGGAGGGGACAACAGAAGAGATCTGCCCCAAGGGGACCACACACTGTTATGAT CCAGCCAGGTTGCAACCTGCTCAATGGGACACAGGAAATTGGGCCCGTGGGTATGACTGAGA ACTGCAATAGGAAAGATTTTCTGACCTGTCATCGGGGGACCACCATTATGACACACGGAAAC TTGGCTCAAGAACCCACTGATTGGACCACATCGAATACCGAGATGTGCGAGGTGGGGCAGGT GTGTCAGGAGACGCTGCTGCTCATAGATGTAGGACTCACATCAACCCTGGTGGGGACAAAAG GCTGCAGCACTGTTGGGGCTCAAAATTCCCAGAAGACCACCATCCACTCAGCCCCTCCTGGG GTGCTTGTGGCCTCCTATACCCACTTCTGCTCCTCGGACCTGTGCAATAGTGCCAGCAGCAG CAGCGTTCTGCTGAACTCCCTCCTCCTCAAGCTGCCCCTGTCCCAGGAGACCGGCAGTGTC CTACCTGTGTGCAGCCCCTTGGAACCTGTTCAAGTGGCTCCCCCGAATGACCTGCCCCAGG GGCGCCACTCATTGTTATGATGGGTACATTCATCTCTCAGGAGGTGGGCTGTCCACCAAAAT GAGCATTCAGGGCTGCGTGGCCCAACCTTCCAGCTTCTTGTTGAACCACACCAGACAAATCG GGGGCTGAGGGCCTGGAGTCTCTCACTTGGGGGGTGGGGCTGGCACTGGCCCCAGCGCTGTG GTGGGGAGTGGTTTGCCCTTCCTGCTAACTCTATTACCCCCACGATTCTTCACCGCTGCTGA CCACCCACACTCAACCTCCCTCTGACCTCATAACCTAATGGCCTTGGACACCAGATTCTTTC ACACTGGGGAGAGCCTGGAGCATCCGGACTTGCCCTATGGGAGAGGGGACGCTGGAGGAGTG GCTGCATGTATCTGATAATACAGACCCTGTCCTTTCA

Page 277 of 359

WO 02/08288 PCT/US01/21066

164/246

FIGURE 162

></usr/seqdb2/sst/DNA/Dnasegs.min/ss.DNA59847

><subunit 1 of 1, 437 aa, 1 stop

><MW: 46363, pI: 6.22, NX(S/T): 3

MSAVLLLALLGFILPLPGVOALLCOFGTVOHVWKVSDLPROWTPKNTSCDSGLGCODTLM LIESGPOVSLVLSKGCTEAKDOEPRVTEHRMGPGLSLISYTFVCROEDFCNNLVNSLPLW APQPPADPGSLRCPVCLSMEGCLEGTTEEICPKGTTHCYDGLLRLRGGGIFSNLRVOGCM POPGCNLLNGTOEIGPVGMTENCNRKDFLTCHRGTTIMTHGNLAOEPTDWTTSNTEMCEV GQVCQETLLLIDVGLTSTLVGTKGCSTVGAONSOKTTIHSAPPGVLVASYTHFCSSDLCN SASSSVLLNSLPPOAAPVPGDROCPTCVOPLGTCSSGSPRMTCPRGATHCYDGYIHLSG GGLSTKMSIQGCVAQPSSFLLNHTROIGIFSAREKRDVOPPASOHEGGGAEGLESLTWGV GLALAPALWWGVVCPSC

Important features of the protein: Signal peptide:

Amino acids

WCG268268 [IB#7/E-AVO6206286 opc.]

1-15

Transmembrane domain:

Amino acids 243-260

N-glycosylation sites:

Amino acids 46-50;189-193;382-386

Glycosaminoglycan attachment sites:

Amino acids 51-55;359-363

N-myristovlation sites:

Amino acids 54-60;75-81;141-147;154-160;168-174;169-175; 198-204;254-260;261-267;269-275;284-290;333-339

347-353;360-366;361-367;388-394;408-414;419-425

Page 278 of 359

WC0268268 [He://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

165/246

FIGURE 163

 ${\tt AGCATAAGAGACTGCCCTGCTTGGTGTTTTGCAGG} \underline{{\tt ATG}} \underline{{\tt ATG}} \underline{{\tt ATG}} \underline{{\tt ATG}} \underline{{\tt GCCCTTCGAGGAGCTTCTGCATTGCTGGTT}}$ CTGTTCCTTGCAGCTTTTCTGCCCCCGCCGCAGTGTACCCAGGACCCAGCCATGGTGCATTACATCTACCAGCG CTTTCGAGTCTTGGAGCAAGGGCTGGAAAAATGTACCCAAGCAACGAGGGCATACATTCAAGAATTCCAAGAGT TCTCAAAAAATATATCTGTCATGCTGGGAAGATGTCAGACCTACACAAGTGAGTACAAGAGTGCAGTGGGTAAC CGTATCAGAGGACAAGACACTGGCAGAAATGTTGCTCCAAGAAGCTGAAGAAGAAAAAGATCCGGACTCTGC TGAATGCAAGCTGTGACAACATGCTGATGGGCATAAAGTCTTTGAAAATAGTGAAGAAGATGATGGACACACAT GGCTCTTGGATGAAGATGCTGTCTATAACTCTCCAAAGGTGTACTTATTAATTGGATCCAGAAACAACACTGT TTGGGAATTTGCAAACATACGGGCATTCATGGAGGATAACACCAAGCCAGCTCCCCGGAAGCAAATCCTAACAC TTTCCTGGCAGGGAACAGGCCAAGTGATCTACAAAGGTTTTCTATTTTTCATAACCAAGCAACTTCTAATGAG ATAATCAAATATAACCTGCAGAAGAGACGACTGTGGAAGATCGAATGCTGCTCCCAGGAGGGGTAGGCCGAGCATT GGTTTACCAGCACTCCCCCTCAACTTACATTGACCTGGCTGTGGATGAGCATGGGCTCTGGGCCATCCACTCTG GGCCAGGCACCCATAGCCATTTGGTTCTCACAAAGATTGAGCCGGGCACACTGGGAGTGGAGCATTCATGGGAT ACCCCATGCAGAAGCCAGGATGCTGAAGCCTCATTCCTCTTGTGTGGGGTTCTCTATGTGGTCTACAGTACTGGGGCCCAGGGCCCTCATCGCATCACCTGCATCTATGATCACTGGGCACTATCAGTGAGGAGGACTTGCCCAACT TGTTCTTCCCCAAGAGACCAAGAAGTCACTCCATGATCCATTACAACCCCAGAGATAAGCAGCTCTATGCCTGG AATGAAGGAAACCAGATCATTTACAAACTCCAGACAAAGAGAAAGCTGCCTCTGAAG<u>TAA</u>TGCATTACAGCTGT GAGAAAGAGCACTGTGGCTTTGGCAGCTGTTCTACAGGACAGTGAGGCTATAGCCCCTTCACAATATAGTATCC CTCTAATCACACAGGAAGAGTGTGTAGAAGTGGAAATACGTATGCCTCCTTTCCCAAATGTCACTGCCTTAG GTAT CTTCCAAGAGCTTAGATGAGAGCATATCATCAGGAAAGTTTCAACAATGTCCATTACTCCCCCAAACCTC CTGGCTCTCAAGGATGACCACATTCTGATACAGCCTACTTCAAGCCTTTTGTTTTACTGCTCCCCAGCATTTAC TGTAACTCTGCCATCTTCCCTCCCACAATTAGAGTTGTATGCCAGCCCCTAATATTCACCACTGGCTTTTCTCT CCCCTGGCCTTTGCTGAAGCTCTTCCCTCTTTTTCAAATGTCTATTGATATTCTCCCATTTTCACTGCCCAACT CTCAAACTCCAGAGCTCAAGAGATCCTCCTGCCTCAGCCTCCTAAGTACCTGGGATTACAGGCATGTGCCACCA CACCTGGCTTAAAATACTATTCTTATTGAGGTTTAACCTCTATTTCCCCTAGCCCTGTCCTTCCACTAAGCTT GGTAGATGTAATAAAAGTGAAAATATTAACATTTGAATATCGCTTTCCAGGTGTGGAGTGTTTGCACATCAT TGAATTCTCGTTTCACCTTTGTGAAACATGCACAAGTCTTTACAGCTGTCATTCTAGAGTTTAGGTGAGTAACA CAATTACAAAGTGAAAGATACAGCTAGAAAATACTACAAATCCCATAGTTTTTCCATTGCCCAAGGAAGCATCA AATACGTATGTTTGTTCACCTACTCTTATAGTCAATGCGTTCATCGTTTCAGCCTAAAAATAATAGTCTGTCCC TTTAGCCAGTTTTCATGTCTGCACAAGACCTTTCAATAGGCCTTTCAAATGATAATTCCTCCAGAAAACCAGTC ATAAAAGTGACACTGAGCAAAAAAAAAAAAAAA

WC0208268 [Me://E/WO0206286 opc]

WO 02/08288

PCT/US01/21066

Page 279 of 359

166/246

FIGURE 164

MOVALROASALULFLAAFLPPPOCTOPPAMMIYTYORRRVLEGGEBKCTQATRAYTOEFQEFSKNISVULGKC OTYTSEKKSAVONLARUEKRAGREDITYGYLERABDECIVESDRITLABHLIQEABEBKKITRILABACINMIMOI KSLKIVKKMMDTHGSMMKDAVYNSFKVYLLIGSKNNTYWEFANIRATMEDNYKFAPRKGILTLSWOGTGOVITK GELFFRNGATRISHEITKYNLGKRYEDDRILLDGGVGRALVYGRSESTYTLDLADDBEGMATHISGGFTSHLULTK IEPGTLGVEHSWDTPCRSQDAEASFILLGULYVYYSTGGQGPHRITCIYDPLGTISEEDLPNLFFFKRPRSHSM HYMPROKQULYMNEGOGITYKLGYFKKDLE

Page 230 of 359

WO0268268 [He://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

167/246

FIGURE 165

 $\tt TTCACCCCAAGTGACC\underline{ATG} AGAGGTGCCACGCGAGTCTCAATCATGCTCCTAGTAACTGTGTCTGACTGTG$ CTGTGAT CACAGGGGCCTGTGAGCGGGATGTCCACTGTGGGGCACCTGCTGTGCCATCAGCCTGTGGCTT CGAGGGCTGCGGATGTGCACCCCGCTGGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTT $\tt CTTCAGGAAACGCAAGCACCACCTGTCCTTGCTTGCCCAACCTGCTGCTCCAGGTTCCCGGACGGCAGGT$ ACCGCTGCTCCATGGACTTGAAGAACATCAATTTTTAGGCGCTTGCCTGGTCTCAGGATACCCACCATCCTTTT CCTGAGCACAGCCTGGATTTTTATTTCTGCCATGAAACCCAGCTCCCATGACTCTCCCAGTCCCTACACTGACT ACCCTGATCTCTCTTGTCTAGTACGCACATATGCACACAGGCAGACATACCTCCCATCATGACATGGTCCCCAG GCTGGCCTGAGGATGTCACAGCTTGAGGCTGTGTGAAAGGTGGCCAGCCTGGTTCTCTCCCTGCTCAGGC TGCCAGAGAGGTGGTAAATGGCAGAAAGGACATTCCCCCTCCCCCCCGGTGACCTGCTCTCTTTCCTGGGC $\tt CCTGCCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAGACATTCCTGGGCACAGGCTCTTGGGTGCATTGCT$ TCTTCCCTCGATTGGTTAACTCCTTAGTTTCAGACCACAGACTCAAGATTGGCTCTTCCCAGAGGGCAGCAGAC AGTCACCCCAAGGCAGGTGTAGGGAGCCCAGGGAGGCCAATCAGCCCCCTGAAGACTCTGGTCCCAGTCAGCCT GTGGCTTGTGGCCTGTGACCTTCTGCCAGAATTGTCATGCCTCTGAGGCCCCCTCTTACCACACTTT ACCAGTTAACCACTGAAGCCCCCAATTCCCACAGCTTTTCCATTAAAATGCAAATGGTGGTGGTTCAATCTAAT CTGATATTGACATATTAGAAGGCAATTAGGGTGTTTCCTTAAACAACTCCTTTCCAAGGATCAGCCCTGAGAGC AGGTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGGTGGGAGCAGGGACAGGGACAGGGCAGGGCAGGG GCTGAAAGGGGCACTGATTCAGACCAGGGAGGCAACTACACACCCAACATGCTGGCTTTAGAATAAAAGCACCAA CTGAAAAAA

WCccsones the WE AN Oraclesse card

WO 02/08288 PCT/US01/21066

168/246

FIGURE 166

 $\label{thm:magatrvsimill} $$\operatorname{MRGATRVSIMLLLYTVSDCAVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEECHPGSHKVPFFRKRK$$ $$\operatorname{HHTCPCLPNLLCSRFPDGRYRCSMDLKNINF}$$

Important feratures: Signal peptide: amino acids 1-19

Tyrosine kinase phosphorylation site: amino acids 88-95

N-myristoylation sites: amino acids 33-39, 35-41, 46-52

Page 232 of 359

PCT/US01/21066

WCG268268 (IB#7/E-AVO6206286 opc.)

WO 02/08288

169/246

FIGURE 167

AACTCAAACTCCTCTCTGGGAAAACGCGGTGCTTGCTCCTCCCGGAGTGGCCTTGGCAGGGTGTTGGAGCCC TCGGTCTGCCCCGTCCGGTCTCTGGGGCCAAGGCTGGGTTTCCCTCATGTATGGCAAGAGCTCTACTCGTGCGG TGCTTCTTCTCCTTGGCATACAGCTCACAGCTCTTTGGCCTATAGCAGCTGTGGAAATTTATACCTCCCGGGTG CTGGAGGCTGTTAATGGGACAGATGCTCGGTTAAAATGCACTTTCTCCAGCTTTGCCCCTGTGGGTGATGCTCT AACAGTGACCTGGAATTTTCGTCCTCTAGACGGGGGACCTGAGCAGTTTGTATTCTACTACCACATAGATCCCT TCCAACCCATGAGTGGGCGGTTTAAGGACCGGGTGTCTTGGGATGGGAATCCTGAGCGGTACGATGCCTCCATC CTTCTCTGGAAACTGCAGTTCGACGACAATGGGACATACACCTGCCAGGTGAAGAACCCACCTGATGTTGATGG GGTGATAGGGGAGATCCGGCTCAGCGTCGTGCACACTGTACGCTTCTCTGAGATCCACTTCCTGGCTCTGGCCA TTGGCTCTGCCTGTGCACTGATGATCATAATAGTAATTGTAGTGGTCCTCTTCCAGCATTACCGGAAAAAGCGA TGGGCCGAAAGAGCTCATAAAGTGGTGGAGATAAAATCAAAAGAAGAGGAAAGGCTCAACCAAGAGAAAAAGGT CTCTGTTTATTTAGAAGACACAGACTAACAATTTTAGATGGAAGCTGAGATGATTTCCAAGAACAAGAACCCTA GTATTTCTTGAAGTTAATGGAAACTTTTCTTTGGCTTTTCCAGTTGTGACCCGTTTTCCAACCAGTTCTGCAGC ATATTAGATTCTAGACAAGCAACACCCCTCTGGAGCCAGCACAGTGCTCCTCCATATCACCAGTCATACACAGC CTCATTATTAAGGTCTTATTTAATTTCAGAGTGTAAATTTTTTCAAGTGCTCATTAGGTTTTATAAACAAGAAG CTACATTTTTGCCCTTAAGACACTACTTACAGTGTTATGACTTGTATACACATATATTGGTATCAAAGGGGATA AAAGCCAATTTGTCTGTTACATTTCCTTTCACGTATTTCTTTTAGCAGCACTTCTGCTACTAAAGTTAATGTGT TTACTCTCTTCCCACATTCTCAATTAAAAGGTGAGCTAAGCCTCCTCGGTGTTTCTGATTAACAGTAAA TGAATTTCTTTCAATATTCCAGGTGATAGATTTTTGTCG

M_CGC08058 (igs: N, E. VA.Oxxxxxx obc) Eude 3g3 of 3g8

WO 02/08288 PCT/US01/21066

170/246

FIGURE 168

MYGKSSTRAVILLIGIQLTALMPIAAVEIYTSRVLEAVNGTDARIKCTFSSFAPVGDALTVTWNFRPLDGGPEQ FVFYYHIDFPGPWSGRYENGYSWOGNEBYRDASILLIMKLÖFDDDGTYTQCVKNPPDVDGVIGSIRLSVVHTVRF SEHHFLALAIGSACALMIIVIVVVLFGHYRKRWAERAHKVVEIKSREGERLNGEKKUSVYLEDTD WC6268368 [Her//E/W/06266286 opc]

WO 02/08288 PCT/US01/21066

Page 234 of 359

171/246

FIGURE 169

GAGCGAACATGGCAGCGCGTTGGCGGTTTTGGTGTCTCTGTGACCATGGTGGTGGCGCTG CTCATCGTTTGCGACGTTCCCTCAGCCTCTGCCCAAAGAAGAAGGAGATGGTGTTATCTGA AGTTCCGTCGCCTTGTGAAAGCCCCACCGAGAAATTACTCCGTTATCGTCATGTTCACTGCT CTCCAACTGCATAGACAGTGTGTCGTTTGCAAGCAAGCTGATGAAGAATTCCAGATCCTGGC AAACTCCTGGCGATACTCCAGTGCATTCACCAACAGGATATTTTTTTGCCATGGTGGATTTTG ATGAAGGCTCTGATGTATTTCAGATGCTAAACATGAATTCAGCTCCAACTTTCATCAACTTT CCTGCAAAAGGGAAACCCAAACGGGGTGATACATATGAGTTACAGGTGCGGGGTTTTTCAGC TGAGCAGATTGCCCGGTGGATCGCCGACAGAACTGATGTCAATATTAGAGTGATTAGACCCC CAAATTATGCTGGTCCCCTTATGTTGGGATTGCTTTTTGGCTGTTATTGGTGGACTTGTGTAT CTTCGAAGAAGTAATATGGAATTTCTCTTTAATAAAACTGGATGGGCTTTTGCAGCTTTGTG TTTTGTGCTTGCTATGACATCTGGTCAAATGTGGAACCATATAAGAGGACCACCATATGCCC ATAAGAATCCCCACACGGGACATGTGAATTATATCCATGGAAGCAGTCAAGCCCAGTTTGTA GCTGAAACACACTTGTTCTTCTGTTTAATGGTGGAGTTACCTTAGGAATGGTGCTTTTATG GACTTGTTGTATTATTCTTCAGTTGGATGCTCTCTATTTTTAGATCTAAATATCATGGCTAC CCATACAGCTTTCTGATGAGTTAAAAAGGTCCCAGAGATATATAGACACTGGAGTACTGGAA ATTGAAAAACGAAAATCGTGTGTGTTTGAAAAGAAGAATGCAACTTGTATATTTTGTATTAC CTCTTTTTTCAAGTGATTTAAATAGTTAATCATTTAACCAAAGAAGATGTGTAGTGCCTTA ACAAGCAATCCTCTGTCAAAATCTGAGGTATTTGAAAATAATTATCCTCTTAACCTTCTCTT CCCAGTGAACTTTATGGAACATTTAATTTAGTACAATTAAGTATATTATAAAAATTGTAAAA CTACTACTTTGTTTTAGTTAGAACAAAGCTCAAAACTACTTTAGTTAACTTGGTCATCTGAT TTTATATTGCCTTATCCAAAGATGGGGAAAGTAAGTCCTGACCAGGTGTTCCCACATATGCC TGTTACAGATAACTACATTAGGAATTCATTCTTAGCTTCTTCATCTTTGTGTGGATGTGTAT ACTTTACGCATCTTTCCTTTTGAGTAGAGAAATTATGTGTGTCATGTGGTCTTCTGAAAATG GAACACCATTCTTCAGAGCACACGTCTAGCCCTCAGCAAGACAGTTGTTTCTCCTCCTCCTT TCTCTAAATACAGGATTATAATTTCTGCTTGAGTATGGTGTTAACTACCTTGTATTTAGAAA GATTTCAGATTCATTCCATCTCCTTAGTTTTCTTTTAAGGTGACCCATCTGTGATAAAAATA TAGCTTAGTGCTAAAATCAGTGTAACTTATACATGGCCTAAAATGTTTCTACAAATTAGAGT TTGTCACTTATTCCATTTGTACCTAAGAGAAAAATAGGCTCAGTTAGAAAAGGACTCCCTGG GAGGTCAGGAGTTCGAGACCATCCTGGCCAACATGGTGAAACCCCGTCTCTACTAAAAATAT AAAAATTAGCTGGGTGTGGCAGGAGCCTGTAATCCCAGCTACACAGGAGGCTGAGGCAC GAGAATCACTTGAACTCAGGAGATGGAGGTTTCAGTGAGCCGAGATCACGCCACTGCACTCC

PCT/US01/21066

Page 235 of 359

WO 02/08288

172/246

FIGURE 170

MAARWKFWCVSVTMVVALLIVCDVPSASAQRKKEMVLSEKVSOLMEWYNKRPVIRMNGDKFR RIVKAPPRNYSVIVMFTALQLHRQCVVCKQADBEFQILANSWRYSSAFTNRIFFAMVDFDEG SDVFQMLNNNSAPTFINFPARGKFKRGDTYELQVRGFSABQIARWIADRTDVNITAVIRPPNY AGPLMLGLLLAVIGGLVYLRRSNMEFLFNKTGWAFAALCFVLAMTSGQMWHHIRGPPYAHKN PHTGHVNYHHGSSQAQFVAETHIVLLFNGGVTLGMVLLCEAATSDMDIGKRKIMCVAGIGLV VLFFSWMLSIFFSKYHGYPYSFLMS

Signal peptide:

amino acids 1-29

Transmembrane domains:

amino acids 183-205, 217-237, 217-287, 301-321

WO0268268 [He://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 236 of 359

173/246

FIGURE 171

WCG208268 [Ner//E/W/Q0206286 opc]

PCT/US01/21066

Page 237 of 359

174/246

FIGURE 172

 ${\tt MAPRGCIVAVFAIFCISRLLCSHGAPVAPMTPYLMLCQPHKRCGDKFYDPLQHCCYDDAVVPLARTQTCGNCTFRVCFEQCCPWTFMVKLINQNCDSARTSDDRLCRSVS}$

Important features: Signal peptide: amino acids 1-24

WO 02/08288

Page 288 of 359

WCG268268 (IB#7/E-AV-06206286 opc.)

WO 02/08288 PCT/US01/21066

175/246

FIGURE 173

GCGCGTCCGACGCGACATGGGCGTCCCCACGGCCCTGGAGGCCGGCAGCTGGCGCTGGGGA TCCCTGCTCTTCGCTCTCTCCTGGCTGCGTCCCTAGGTCCGGTGGCAGCCTTCAAGGTCGC CACGCCGTATTCCCTGTATGTCTGTCCCGAGGGGCAGAACGTCACCCTCACCTGCAGGCTCT TGGGCCCTGTGGACAAAGGGCACGATGTGACCTTCTACAAGACGTGGTACCGCAGCTCGAGG GGCGAGGTGCAGACCTGCTCAGAGCGCCGGCCCATCCGCAACCTCACGTTCCAGGACCTTCA CCTGCACCATGGAGGCCACCAGGCTGCCAACACCAGCCACGACCTGGCTCAGCGCCACGGGC TGGAGTCGGCCTCCGACCACGATGGCAACTTCTCCATCACCATGCGCAACCTGACCCTGCTG GATAGCGGCCTCTACTGCTGCTGGTGGTGGAGATCAGGCACCACCACTCGGAGCACAGGGT CCATGGTGCCATGGAGCTGCAGGTGCAGACAGGCAAAGATGCACCATCCAACTGTGTGGTGT ACCCATCCTCCCCAGGATAGTGAAAACATCACGGCTGCAGCCCTGGCTACGGGTGCCTGC CTCCAACCGCCGTGCCCAGGAGCTGGTGCGGATGGACAGCAACATTCAAGGGATTGAAAACC CCGGCTTTGAAGCCTCACCACCTGCCCAGGGGATACCCGAGGCCAAAGTCAGGCACCCCCTG TCCTATGTGGCCCAGCGCAGCCTTCTGAGTCTGGGCGGCATCTGCTTTCGGAGCCCAGCAC CCCCTGTCTCCTCCAGGCCCCGGAGACGTCTTCTTCCCATCCCTGGACCCTGTCCCTGACT CTCCAAACTTTGAGGTCATCTAGCCCAGCTGGGGGACAGTGGGCTGTTGTGGCTGGGTCTGG GGCAGGTGCATTTGAGCCAGGGCTGGCTCTGTGAGTGGCCTCCTTGGCCTCGGCCCTGGTTC CCTCCCTCCTGCTCTGGGCTCAGATACTGTGACATCCCAGAAGCCCAGCCCTCAACCCCTC TGGATGCTACATGGGGATGCTGGACGCCTCAGCCCCTGTTCCAAGGATTTTTGGGGTGCTGAG ATTCTCCCCTAGAGACCTGAAATTCACCAGCTACAGATGCCAAATGACTTACATCTTAAGAA GTCTCAGAACGTCCAGCCCTTCAGCAGCTCTCGTTCTGAGACATGAGCCTTGGGATGTGGCA GCATCAGTGGGACAAGATGGACACTGGGCCACCCTCCCAGGCACCAGACACAGGGCACGGTG GAGAGACTTCTCCCCCGTGGCCGCCTTGGCTCCCCGTTTTGCCCGAGGCTGCTCTTCTGTC ACCTTCCCCAGCTGCCTCCTACCAGCAGTTTCTCTGAAGATCTGTCAACAGGTTAAGTCAAT CTGGGGCTTCCACTGCCTGCATTCCAGTCCCCAGAGCTTGGTGGTCCCGAAACGGGAAGTAC ATATTGGGGCATGGTGGCCTCCGTGAGCAAATGGTGTCTTGGGCAATCTGAGGCCAGGACAG GTGGAGAGGGGCACCTGCCCCCGCCCTCCCCATCCCCTACTCCCACTGCTCAGCGCGGGCC ATTGCAAGGGTGCCACACATGTCTTGTCCACCCTGGGACACTTCTGAGTATGAAGCGGGAT

Page 239 of 359

PCT/US01/21066

176/246

FIGURE 174

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA64897
><subunit 1 of 1, 311 aa, 1 stop</pre>

><MW: 33908, pI: 6.87, NX(S/T): 6

MGVPTALEAGSWRWGSLLFALFILASIGPVAAFKVATPYSLVVCEEGONVTLTCRLLEPVDK GHDVTFYKTWYRSSRGEVQTCSERPIRNLTFQDLHLHHGGHQANNTSHDLAQRHGLESASD HHGNF5ITWRNLTLLDSGLYCCLVVEIRHHSBHRVHGAMELQVQTGKDAFSNCVVYFSSG DSENITAAALATGACIVGILCLPLILLLVYKGRQAASNRRAQELVRMDSNIQGIENFGFBAS PPAQGIPEAKVRHPLSYVQRQFSESGRRHLISEPSTPLSPFGGDVFFFSLDFVPDSPNFFEVI

Signal peptide: amino acids 1-28

WO 02/08288

WC0268268 [Be://E-W/00206286 opc]

Transmembrane domain: amino acids 190-216

WCG268268 [IB#7/E-AVO6206286 opc.]

WO 02/08288 PCT/US01/21066

Page 290 of 359

177/246

FIGURE 175

Page 291 of 359

178/246

FIGURE 176

 $\verb|MDSLRKMLISVAMLGAGAGVGYALLVIVTPGERRKQEMLKEMPLQDPRSREEAARTQQLLLATLQEAATTQENVAWRKNWMVGGEGGASGRSP|$

Important features: Signal peptide: amino acids 1-18

WCG208268 [He://E-/W/00206286 opc]

Page 292 of 359

WCG268268 (IB#7/E-AVO6206286 opc.)

WO 02/08288 PCT/US01/21066

179/246

FIGURE 177

GCCAGGCAGGTGGGCCTCAGGAGGTGCCTCCAGGCGGCCAGTGGGCCTGAGGCCCCAGCAAG GGCTAGGGTCCATCTCCAGTCCCAGGACACAGCAGCGGCCACCATGGCCACGCCTGGGCTCC AGCAGCATCAGAGCAGCCCCTGTGGTTGGCAGCAAAGTTCAGCTTGGCTGGGCCCGCTGTGA GGGGCTTCGCGCTACGCCCTGCGGTGTCCCGAGGGCTGAGGTCTCCTCATCTTCTCCCTAGC AGTGGATGAGCAACCCAACGGGGGCCCGGGGGGGGAACTGGCCCCGAGGGAGAGCACCCC AAAGCCACATCTGTAGCCAGGATGAGCAGTGTGAATCCAGGCAGCCCCCAGGACCGGGGAGG CACAGGTGGCCCCACCACCGGAGGAGCAGCTCCTGCCCCTGTCCGGGGGATGACTGATTC TCCTCCGCCAGGCCACCCAGAGGAAGGCCACCCCGCCTGGAGGCACAGGCCATGAGGGGC TCTCAGGAGGTGCTGCTGATGTGGCTTCTGGTGTTGGCAGTGGGCGGCACAGAGCACGCCTA CCGGCCGGCCGTAGGGTGTGTGCTGTCCGGGCTCACGGGGACCCTGTCTCCGAGTCGTTCG TGCAGCGTGTGTACCAGCCCTTCCTCACCACCTGCGACGGGCACCGGGCCTGCAGCACCTAC CGAACCATCTATAGGACCGCCTACCGCCGCAGCCCTGGGCTGGCCCTGCCAGGCCTCGCTA CGCGTGCTGCCCCGGCTGGAAGAGGACCAGCGGGCTTCCTGGGGCCTGTGGAGCAGCAATAT GCCAGCCGCCATGCCGGAACGGAGGGAGCTGTCCAGCCTGGCCGCTGCCGCTGCCCTGCA GGATGGCGGGTGACACTTGCCAGTCAGATGTGGATGAATGCAGTGCTAGGAGGGGCGGCTG TCCCCAGCGCTGCATCAACACCGCCGGCAGTTACTGGTGCCAGTGTTGGGAGGGGCACAGCC TGTCTGCAGACGGTACACTCTGTGTGCCCAAGGGAGGGCCCCCCAGGGTGGCCCCCAACCCG ACAGGAGTGGACAGTGCAATGAAGGAAGAAGTGCAGAGGCTGCAGGTCCAGGGTGGACCTGCT GGAGGAGAGCTGCAGCTGGTGCTGGCCCCACTGCACAGCCTGGCCTCGCAGGCACTGGAGC ATGGGCTCCCGGACCCCGGCAGCCTCCTGGTGCACTCCTTCCAGCAGCTCGGCCGCATCGAC CTCGTGACTGCCCAGCGCTCCAGGCTGGACTGAGCCCCTCACGCCCCCTGCAGCCCCCATG CCCCTGCCCAACATGCTGGGGGTCCAGAAGCCACCTCGGGGTGACTGAGCGGAAGGCCAGGC AGGGCCTTCCTCCTCTCCTCCCCTTCCTCGGGAGGCTCCCCAGACCCTGGCATGGGAT GGGCTGGGATCTTCTCTGTGAATCCACCCCTGGCTACCCCACCCTGGCTACCCCAACGGCA TCCCAAGGCCAGGTGGACCCTCAGCTGAGGGAAGGTACGAGCTCCCTGCTGGAGCCTGGGAC CCATGGCACAGGCCAGGCCCGGAGGCTGGGTGGGGCCTCAGTGGGGGCTGCTGCCTGAC CCCCAGCACAATAAAAATGAAACGTG

M_C0008088 figs NLE vs.Octobesag ober 1

WO 02/08288 PCT/US01/21066

180/246

FIGURE 178

MRGSQEVLLMWILLVLAVGGTEHAYRPCRRVCAVRAHGDPVSESFYQRYYQPFLTTCDGHRAC STYRTIYRTAYRRSPGLAPARPRYACCPGWKRTSGLPGACGAAICQPPCRNGGSCVQPGRCR CPAGWRGDTCQSDVDECSARRGGCPQRCINTAGSYWCQCWEGHSLSADGTLCVPKGGPRVA PNETGVDSAMKEEVQRLQSRVDLLEEKLQLVLAPLHSLASQALEHGLPDPGSLLVHSFQQLG RIDSLSEGISFLEEGLGSCSCKKDS

Signal sequence:

1-19

Page 294 of 359

WC6268368 [Her//E/W/06266286 opc]

181/246

FIGURE 179

GACAGCTGTGTCTCGATGGAGTAGACTCTCAGAACAGCGCAGTTTGCCCTCCGCTCACGCAG CCGTCACCTCTCTGTCATCCGTTTCCATGCCGTGAGGTCCATTCACAGAACACATCCATGG CTCTCATGCTCAGTTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGCCAGTGGCAGGTGTTT GGGCCAGACAAGCCTGTCCAGGCCTTGGTGGGGGAGGACGCAGCATTCTCCTGTTTCCTGTC TCCTAAGACCAATGCAGAGGCCATGGAAGTGCGGTTCTTCAGGGGCCAGTTCTCTAGCGTGG TCCACCTCTACAGGGACGGGAAGGACCAGCCATTTATGCAGATGCCACAGTATCAAGGCAGG ACAAAACTGGTGAAGGATTCTATTGCGGAGGGGGCGCATCTCTCTGAGGCTGGAAAACATTAC TGTGTTGGATGCTGGCCTCTATGGGTGCAGGATTAGTTCCCAGTCTTACTACCAGAAGGCCA TCTGGGAGCTACAGGTGTCAGCACTGGGCTCAGTTCCTCATTTCCATCACGGGATATGTT GATAGAGACATCCAGCTACTCTGTCAGTCCTCGGGCTGGTTCCCCCGGCCCACAGCGAAGTG TGTTTGATGTGGAGATCTCTCTGACCGTCCAAGAGAACGCCGGGAGCATATCCTGTTCCATG CGGCATGCTCATCTGAGCCGAGAGGTGGAATCCAGGGTACAGATAGGAGATACCTTTTTCGA GCCTATATCGTGGCACCTGGCTACCAAAGTACTGGGAATACTCTGCTGTGGCCTATTTTTTG GCATTGTTGGACTGAAGATTTCTTCTCCCAAATTCCAGTGGAAAATCCAGGCGGAACTGGAC TGGAGAAGAAGCACGGACAGCCAGAATTGAGAGACGCCCGGAAACACGCAGTGGAGGTGAC TCTGGATCCAGAGACGCTCACCCGAAGCTCTGCGTTTCTGATCTGAAAACTGTAACCCATA GAAAAGCTCCCCAGGAGGTGCCTCACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCT TCTCAGAGTTTCCAAGCAGGGAAACATTACTGGGAGGTGGACGGAGGACAATAAAAGGTG GCGCGTGGGAGTGTGCCGGGATGATGTGGACAGGAGGAGGAGGAGTACGTGACTTTGTCTCCCG ATCATGGGTACTGGGTCCTCAGACTGAATGGAGAACATTTGTATTTCACATTAAATCCCCGT TTTATCAGCGTCTTCCCCAGGACCCCACCTACAAAAATAGGGGTCTTCCTGGACTATGAGTG TTGAAGGCTTATTGAGGCCCTACATTGAGTATCCGTCCTATAATGAGCAAAATGGAACTCCC ATAGTCATCTGCCCAGTCACCCAGGAATCAGAGAAAGAGGCCTCTTGGCAAAGGGCCTCTGC AATCCCAGAGACAACCACTGAGTCCTCCTCACAGGCAACCACGCCCTTCCTCCCCAGGG GATCCAAAGTCCCGCAGCAGCCGGCCAAGGTGGCTTCCAGATGAAGGGGGACTGGCCTGTCC AGTTTGCTCTCACTCCATCTGGCTAAGTGATCTTGAAATACCACCTCTCAGGTGAAGAACCG TCAGGAATTCCCATCTCACAGGCTGTGGTGTAGATTAAGTAGACAAGGAATGTGAATAATGC TTAGATCTTATTGATGACAGAGTGTATCCTAATGGTTTGTTCATTATATTACACTTTCAGTA AAAAAA

Page 295 of 359

182/246

FIGURE 180

MALMLSLVLSLLKLGSGOWQVFGPDKPVQALVGEDAAFSCFLSPKTNAEAMEVRFFRGQFSS
VYHLYRDGKDQFFMQMPQYQGRTKIJVKDSIAEGRISIREBITVLDAGLYGCRISSGSYYQK
ATWELQVSALGSVPLISTTGVVDRDIQLLCQSSGWFPRFTAKWKGPQGQDLSTDSRYNDMH
GLFDVEISLTVQENAGSISCSMRHAHLSREVESRVQIGDTFFEPISWHLATKVIGILCCGLF
FGIVGLKIFFSKFQMKIQAELDWRRKHGQAELRDARKHAVEVTLDPETAHPKLCVSDLKTVT
HRKAPQEVPHSSKRFTRKSVVASQSFQAGKHYWEVDGGNNKBWFGVCRDDVDRRKBYVTLS
PDHGYWVLRLNGEHLYFTLNPRFISVFPRTPPTKIGVFLDYECGTISFFNINDQSLIYTLTC
RFEGLLRPYIEYPSYNEQNGTPIVICPVTQESEKEASWQRASAIPETSNSESSSQATTPFLP
RGEM

Signal peptide: amino acids 1-17

WC0268268 [He://E-W/00206286 opc]

Transmembrane domain: amino acids 239-255

WC0268268 [He://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 296 of 359

183/246

FIGURE 181

GCGATGCTCCCCCGGTGCCGCTGCCGCCGCCGCTTCCGAGGCTTCCTTGGTCGGATTGCAACGAGAGAAGA TGACTGACCAACCGACTGCTGAATGAATGAATGCCGGAGCCGAGCCCATGAGGAGCCTGCCGAGCCTGGG CCTAGGGCGACGGCTCCCACGGCCCAGGCCCCGAGGACCGGGCCCCCGCGCGCCACCGTCCACCGACCCTGGC TGCGACTTCTCCAGCCCAGTCCCCGGAGACCACCCTCTTTGGGCGACTGCTGGACCCTCTTCCACCACCTTTC AGGCGCCGCTCGGCCCTCGCCGACCACCCCTCCGGCGCGCACTTCGACCACCTCTCAGGCGCCGACC AGACCCGCGCCGACCACCCTTTCGACGACCACCGGCCCCGGCCCCGACCCCCTGTAGCGACCACCGTACCGGC GCCCACGACTCCCCGGACCCCCGATCTCCCCAGCAGCAGCAGCAGCGGCGTCCTCCCCACCCCACCTG CGCTGCAACCAGACCACAGGGCAGTGTGAGTGTCGGCCAGGTTATCAGGGGCTTCACTGTGAAACCTGCAAAGA GGGCTTTTACCTAAATTACACTTCTGGGCTCTGTCAGCCATGTGACTGTAGTCCACATGGAGCTCTCAGCATAC CTCTCAAGGACCATACTGGTTTAAACAAAGGAGGATGAGGGTCATAGATTTACAAAATATTTTATATACTTTTA TTCTCTTACTTTATATGTTATATTTAATGTCAGGATTTAAAAACATCTAATTTACTGATTTAGTTCTTCAAAAG CACTAGAGTCGCCAATTTTCTCTGGGATAATTTCTGTAAATTTCATGGGAAAAAATTATTGAAGAATAAATCT GCTTTCTGGAAGGGCTTTCAGGCATGAAACCTGCTAGGAGGTTTAGAAATGTTCTTATGTTTATTAATATACCA TTGGAGTTTGAGGAAATTTGTTGTTTGGTTTATTTTTCTCTCTAATCAAAATTCTACATTTGTTTCTTTGGACA TCTAAAGCTTAACCTGGGGGTACCCTAATTTATTTAACTAGTGGTAAGTAGACTGGTTTTACTCTATTTACCAG TACATTTTTGAGACCAAAAGTAGATTAAGCAGGAATTATCTTTAAACTATTATGTTATTTTGGAGGTAATTTAAT CTAGTGGAATAATGTACTGTTATCTAAGCATTTGCCTTGTACTGCACTGAAAGTAATTATTCTTTGACCTTATG TGAGGCACTTGGCTTTTTGTGGACCCCAAGTCAAAAAACTGAAGAGACAGTATTAAATAATGAAAAAATAATG ACAGGTTATACTCAGTGTAACCTGGGTATAACCCAAGATCTGCTGCCACTTACGAGCTGTGTTCCTTGGGCAAG CTAGCACATGTCACTCAATAAATTCTGGTTTGTTTTAATTTCAAAGGAATATTATGGACTGAAATGAGAGAACA TGTTTTAAGAACTTTTAGCTCCTTGACAAAGAAGTGCTTTATACTTTAGCACTAAATATTTTAAATGCTTTATA AATGATATTATACTGTTATGGAATATTGTATCATATTGTAGTTTATTAAAAATGTAGAAGAGGCTGGGCGCGGT GGCTCACGCCTGTAATCCTAGCACTTTGGGAGGCCAAGGCGGGTGGATCACTTGAGGCCAGGAGTTCTAGATGA GTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGATCGGTTGAACCCGGGAGGTTGCAGTTGCAGTTGAGCTGA

WO 02/08288

Page 297 of 359

184/246

FIGURE 182

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA64952

><subunit 1 of 1, 258 aa, 1 stop

><MW: 25716, pI: 8.13, NX(S/T): 5

MRSLPSLGGLALLCCAAAAAAAAAAAAAASAAAGANTGGGGAAGQVDASSGPGLRGESSHPPFRATA PTAQAPTRGPPRATVHRPLAATSPAQSPETTPLWATAGPSSTTFQAPLGPSPTTPPADERTS TTSQAPTRPAPTTLSTTTGPAPTTPVATTVPAPTTPRTTPTDLPSSSMSSVLPTPPATEAPS SPPPEYVCNCSVVGSLNVNRCNQTTGQCECRPGYQGLHCETCKEGFYLNYTSGLCQPCDCSP HGGLSTPCM

Important features of the protein: Signal peptide:

amino acids 1-25

N-glycosylation sites.

amino acids 30-33, 172-175, 195-198, 208-211, 235-238

EGF-like domain cysteine pattern signature. amino acids 214-226.

Page 298 of 359

WCG268268 (IB#7/E-AV-06206236 opc.)

WO 02/08288 PCT/US01/21066

185/246

FIGURE 183

Page 299 of 359

PCT/US01/21066

186/246

FIGURE 184

MGGLILAAFIAIVSVPRAQAVWLGRLDPEQILGPWYVLAVASREKGFAMEKDMKNVVGVVVTITPENNLRTLSS QHGLGGCDQSVMDLIKRNGGWVFENPSIGVLELWVLAINFRDYAIIFTQLEFGDEPFMTVELYSLTETASQEAM GIFTMYNSEIGFLSQ

Important features: Signal peptide: amino acids 1-20

WO 02/08288

WCG208268 [Re://E/W/00206286 opc]

Page 300 of 359

WO0268268 [He://E-/W/00206286 opc]

187/246

FIGURE 185

GTTCCGCAGATGCAGAGGTTGAGGTGGCTGCGGGACTGGAAGTCATCGGGCAGAGGTCTCACAGCAGCCAAGGA TTCGAGAAGACGCGGCTACTCTGTGGGGCGACGCTCATCGCCCCAGATGGCTCCTGACAGCAGCCCACTGCCT CAAGCCCCGCTACATAGTTCACCTGGGGCAGCACACCTCCAGAAGGAGGGGGGGTGTGAGCAGACCCGGACAG CCACTGAGTCCTTCCCCCACCCCGGCTTCAACAACAGCCTCCCCAACAAAGACCACCGCAATGACATCATGCTG GT GAAGAT GGCATCGCCAGTCTCCATCACCTGGGCTGTGCGACCCTTCACCCTCTCACGCTGTGTCACTGC GCGCCAACAT CACCATCATTGAGCACCAGAAGTGTGAGAACGCCTACCCCGGCAACATCACAGACACCATGGTG TGTGCCAGCGTGCAGGAAGGGGCCAAGGACTCCTGCCAGGGTGACTCCGGGGGCCCTCTGGTCTGTAACCAGTC TCTTCAAGGCATTATCTCCTGGGGCCAGGATCCGTGTGCGATCACCCGAAAGCCTGGTGTCTACACGAAAGTCT TCCATTTCCACTTGGTGTTTGGTTCCTGTTCACTCTGTTAATAAGAAACCCTAAGCCAAGACCCTCTACGAACA TTCTTTGGGCCTCCTGGACTACAGGAGATGCTGTCACTTAATAATCAACCTGGGGTTCGAAATCAGTGAGACCT GGATTCAAATTCTGCCTTGAAATATTGTGACTCTGGGAATGACAACACCTGGTTTGTTCTCTGTTGTATCCCCA AAAAAAAAAAAAAAAAAA

Page 301 of 359

188/246

FIGURE 186

MRIJOLILIALATGIJGGETRIIKGFECKPHSOPMOAALFEKTELLCGATLIAFEMLITAAHCLKERTITUGE HILOKEESCECTRTATESFPEPGFNELSHENDERNDIMLYMASPYSITMAVEPILTISSRCVTAGTSCLISGWG STSSFOLRJPHTLRCANITIIBHOKCENAYPONITOTWWCASVORGGKDSCQDSGGPLVCNQSLQGIISWGQD PCAITREFSVYTKVCKYVDMIGTHWKN

Important features: Signal peptide:

amino acids 1-18

WC0268268 (Mer//E_W/06Z06286 opc.)

Serine proteases, trypsin family, histidine active site. amino acids 58-63

N-glycosylation sites.

amino acids 99-102, 165-168, 181-184, 210-213

Glycosaminoglycan attachment site. amino acids 145-148

Kringle domain proteins.

amino acids 197-209, 47-64

Serine proteases, trypsin family, histidine protein amino acids 199-209, 47-63, 220-243

Apple domain proteins amino acids 222-249, 189-222

Page 302 of 359

WC6268368 [Her//E/W/06266286 opc]

189/246

FIGURE 187

GCTCAAGTGCCCTGCCTTGCCCCACCCAGCCTGGCCAGAGCCCCCTGGAGAAGGAGC TCTCTTCTTGCTTGGCAGCTGGACCAAGGGAGCCAGTCTTGGGCGCTGGAGGGCCTGTCCTG ACCATGGTCCCTGCCTGGCTGTGGCTGTTTGTGTCTCCGTCCCCCAGGCTCTCCCCAAGGC CCAGCCTGCAGAGCTGTCTGTGGAAGTTCCAGAAAACTATGGTGGAAATTTCCCTTTATACC TGACCAAGTTGCCGCTGCCCGTGAGGGGGCTGAAGGCCAGATCGTGCTGTCAGGGGACTCA GGCAAGGCAACTGAGGGCCCATTTGCTATGGATCCAGATTCTGGCTTCCTGCTGGTGACCAG GGCCTGGACCGAGAGGAGCAGCAGGTACCAGCTACAGGTCACCCTGGAGATGCAGGATG GACATGTCTTGTGGGGTCCACAGCCTGTGCTTGTGCACGTGAAGGATGAGAATGACCAGGTG CCCCATTTCTCTCAAGCCATCTACAGAGCTCGGCTGAGCCGGGGTACCAGGCCTGGCATCCC CTTCCTCTCCTTGAGGCTTCAGACCGGGATGAGCCAGGCAACCCGGATCTTCGAT TCCACATCCTGAGCCAGGCTCCAGCCCAGCCTTCCCCAGACATGTTCCAGCTGGAGCCTCGG CTGGGGGCTCTGGCCCTCAGCCCCAAGGGGAGCACCAGCCTTGACCACGCCCTGGAGAGGAC CTACCAGCTGTTGGTACAGGTCAAGGACATGGGTGACCAGGCCTCAGGCCACCAGGCCACTG CCACCGTGGAAGTCTCCATCATAGAGAGCACCTGGGTGTCCCTAGAGCCTATCCACCTGGCA GAGAATCTCAAAGTCCTATACCCGCACCACATGGCCCAGGTACACTGGAGTGGGGGTGATGT GCACTATCACCTGGAGAGCCATCCCCCGGGACCCTTTGAAGTGAATGCAGAGGGAAACCTCT ACGTGACCAGAGAGCTGGACAGAGAGCCCAGGCTGAGTACCTGCTCCAGGTGCGGGCTCAG TGACAACGTGCCTATCTGCCCTCCCCGTGACCCCACAGTCAGCATCCCTGAGCTCAGTCCAC CAGGTACTGAAGTGACTAGACTGTCAGCAGAGGATGCAGATGCCCCCGGCTCCCCCAATTCC CACGTTGTGTATCAGCTCCTGAGCCTGAGCCTGAGGATGGGGTAGAGGGGAGAGCCTTCCA GGTGGACCCCACTTCAGGCAGTGTGACGCTGGGGGTGCTCCCACTCCGAGCAGGCCAGAACA TCCTGCTTCTGGTGCTGGCCATGGACCTGGCAGGCGCAGAGGGTGGCTTCAGCAGCACGTGT GAAGTCGAAGTCGCAGTCACAGATATCAATGATCACGCCCCTGAGTTCATCACTTCCCAGAT TGGGCCTATAAGCCTCCCTGAGGATGTGGAGCCCGGGACTCTGGTGGCCATGCTAACAGCCA TTGATGCTGACCTCGAGCCCGCCTTCCGCCTCATGGATTTTGCCATTGAGAGGGGGAGACACA GAAGGGACTTTTGGCCTGGATTGGGAGCCAGACTCTGGGCATGTTAGACTCAGACTCTGCAA GAACCTCAGTTATGAGGCAGCTCCAAGTCATGAGGTGGTGGTGGTGGTGCAGAGTGTGGCGA AGCTGGTGGGGCCAGGCCCAGGCCCTGGAGCCACGCTGACTGTGCTAGTGGAGAGA GTGATGCCACCCCCAAGTTGGACCAGGAGAGCTACGAGGCCAGTGTCCCCATCAGTGCCCC AGCCGGCTCTTTCCTGCTGACCATCCAGCCCTCCGACCCCATCAGCCGAACCCTCAGGTTCT CCCTAGTCAATGACTCAGAGGGCTGGCTCTGCATTGAGAAATTCTCCGGGGAGGTGCACACC GCCCAGTCCCTGCAGGGCGCCCAGCCTGGGGACACCTACACGGTGCTTGTGGAGGCCCAGGA TACAGCCCTGACTCTTGCCCCTGTGCCCTCCCAATACCTCTGCACACCCCGCCAAGACCATG GCTTGATCGTGAGTGGACCCAGCAAGGACCCCGATCTGGCCAGTGGGCACGGTCCCTACAGC TTCACCCTTGGTCCCAACCCCACGGTGCAACGGGATTGGCGCCTCCAGACTCTCAATGGTTC CCATGCCTACCTTGGCCCTGCATTGGGTGGAGCCACGTGAACACATAATCCCCGTGG TGGTCAGCCACAATGCCCAGATGTGGCAGCTCCTGGTTCGAGTGATCGTGTCGCTGCAAC GTGGAGGGCAGTGCATGCGCAAGGTGGGCCGCATGAAGGCCATGCCCACGAAGCTGTCGGC AGTGGGCATCCTTGTAGGCACCCTGGTAGCAATAGGAATCTTCCTCATCCTCATTTTCACCC ACTGGACCATGTCAAGGAAGAAGGACCCGGATCAACCAGCAGACAGCGTGCCCCTGAAGGCG ACTGTCTGAATGGCCCAGGCAGCTCTAGCTGGGAGCTTGGCCTCTGGCTCCATCTGAGTCCC CTGGGAGAGCCCAGCACCCAAGATCCAGCAGGGGACAGGACAGAGTAGAAGCCCCTCCAT CTGCCTGGGGTGGAGGCACCATCACCAGGCATGTCTGCAGAGCCTGGACACCAAC TTTATGGACTGCCCATGGGAGTGCTCCAAATGTCAGGGTGTTTGCCCAATAATAAAGCCCCA

Page 303 of 359

190/246

FIGURE 188

WYPAMLWILLCYSVPOALPKAQPARLSVEVERNYGGMFPLYLTKLPLPKRGAEGQIVLSGOSG
KATEGPFAMDPDSGFLIVTRALDREQAEYQLQVTLEMQDGHVLWGPQPVLVHVKDENDQVP
HFSQAIYRARLSRGTRPGIPFLFLEASDRDEPGTANSDLRFHILSQAPAQPSPDMFQLEPRL
GALALSPKGSTSLDHALBRTYQLLVQVKDMGDQASGHQATATVEVSIIESTWVSLEFIHLAE
NLKVLYPHHMAQVHWSGDOWYHLESBPPGFFSVNAEGGNLYVTRELDREAQAEVLLQVRAQN
SHGEDYAAPLELHVLVMDENDNVPICPPRDTVSIPELSPFGTEVTRLSAEDADAPGSPNSH
VVYQLLSPEPBGDVGGRAFFQVDTTSSSVTIGTUPLRAEQGNILLVLLAMDLAGABGGFSSTCE
VEVAVYDINDHAPBFITSQIGFISLPEDVBPGTLVAMLTAIDADLEPAFRLMDFAIBRGDTE
GTFGLDWBFDSGHVRLRLCKNLSYEAAPSHEVVVVQSVAKLVGFGFGFGATATVTVLVERV
MPPHKLDGSYRSAVSISAPAGSFLITIQFSDFISTRLRFSLVNDSEGWHLLEKFSGEWHTA
QSLQGAQFGDTYTVLVERQDTALTLAPVPSQYLCTPRQDHGLIVSGPSKDPDLASGHGFYSF
TLGPNFTVGROWRQTINGSHAVLTLALHWEFREHLIFVVVSHNAQMWQLLVRVIVCRONV
EGQCMRKVGRWKGMFTKLSAVGILVGTLVAGIFFLILIFFHWTMSRKKDPDQPABSVPLKATV

Signal peptide: amino acids 1-18

WC0268268 [Be://E-W/00206286 opc]

Transmembrane domain: amino acids 762-784

Page 304 of 359

191/246

WO0268268 [He://E-W/00206286 opc]

FIGURE 189

GACTTTGCTTGAATGTTTACATTTTCTGCTCGCTGTCCTACATATCACAATATAGTGTTCACGTTTTTGTTAAAA GTATGTGAAATTCGTCCCTGGTTTACCCCACAGTCAACTTACAGAGAAGCCACCACTGTTGATTGCAATGACCT CCGCTTAACAAGGATTCCCAGTAACCTCTCTAGTGACACAAGTGCTTCTCTTACAGAGCAATAACATCGCGA AGACT GTGGATGAGCTGCAGCAGCTTTTCAACTTGACTGAACTAGATTTCTCCCAAAACAACTTTACTAACATT AAGGAGGTCGGGCTGGCAAACCTAACCCAGCTCACAACGCTGCATTTGGAGGAAAATCAGATTACCGAGATGAC TGATTACTGTCTACAAGACCTCAGCAACCTTCAAGAACTCTACATCAACCACAACCAAATTAGCACTATTTCTG CTCATGCTTTTGCAGGCTTAAAAAATCTATTAAGGCTCCACCTGAACTCCAACAAATTGAAAGTTATTGATAGT CGCTGGTTTGATTCTACACCCAACCTGGAAATTCTCATGATCGGAGAAAACCCTGTGATTGGAATTCTGGATAT GAACTTCAAACCCCTCGCAAATTTGAGAAGCTTAGTTTTGGCAGGAATGTATCTCACTGATATTCCTGGAAATG CTTTGGTGGGTCTGGATAGCCTTGAGAGCCTGTCTTTTTATGATAACAAACTGGTTAAAGTCCCTCAACTTGCC CTGCAAAAAGTTCCAAATTTGAAATTCTTAGACCTCAACAAAAACCCCATTCACAAAATCCAAGAAGGGGGACTT CAAAAATATGCTTCGGTTAAAAGAACTGGGAATCAACAATATGGGCGAGCTCGTTTCTGTCGACCGCTATGCCC TGGATAACTTGCCTGAACTCACAAAGCTGGAAGCCACCAATAACCCTAAACTCTCTTACATCCACCGCTTGGCT TTCCGAAGTGTCCCTGCTCTGGAAAGCTTGATGCTGAACAACAATGCCTTGAATGCCATTTACCAAAAGACAGT CGAATCCCTCCCAATCTGCGTGAGATCAGTATCCATAGCAATCCCCTCAGGTGTGACTGTGTGATCCACTGGA TTAACTCCAACAAACCAACATCCGCTTCATGGAGCCCCTGTCCATGTTCTGTGCCATGCCGCCCGAATATAAA GGGCACCAGGTGAAGGAAGTTTTAATCCAGGATTCGAGTGAACAGTGCCTCCCAATGATATCTCACGACAGCTT CCCAAATCGTTTAAACGTGGATATCGGCACGGTTTTCCTAGACTGTCGAGCCATGGCTGAGCCAGAACCTG AAATTTACTGGGTCACTCCCATTGGAAATAAGATAACTGTGGAAACCCTTTCAGATAAATACAAGCTAAGTAGC GAAGGTACCTTGGAAATATCTAACATACAAATTGAAGACTCAGGAAGATACACATGTGTTGCCCAGAATGTCCA AGGGGCAGACACTCGGGTGGCAACAATTAAGGTTAACGGGACCCTTCTGGATGGTACCCAGGTGCTAAAAATAT ACGTCAAGCAGACAGAATCCCATTCCATCTTAGTGTCCTGGAAAGTTAATTCCAATGTCATGACGTCAAACTTA AAATGGTCGTCTGCCACCATGAAGATTGATAACCCTCACATAACATATACTGCCAGGGTCCCAGTCGATGTCCA TGAATACAACCTAACGCATCTGCAGCCTTCCACAGATTATGAAGTGTGTCTCACAGTGTCCAATATTCATCAGC AGACT CAAAAGT CAT GCGTAAATGT CACAACCAAAAATGCCGCCTT CGCAGT GGACATCT CTGAT CAAGAAACC AGTACAGCCCTTGCTGCAGTAATGGGGTCTATGTTTGCCGTCATTAGCCTTGCGTCCATTGCTGTTACTTTGC CAAAAGATTTAAGAGAAAAAACTACCACCACTCATTAAAAAAAGTATATGCAAAAAACCTCTTCAATCCCACTAA ATGAGCTGTACCCACCACTCATTAACCTCTGGGAAGGTGACAGCGAGAAAGACAAAGATGGTTCTGCAGACACC $\texttt{AAGCCAACCCAGGTCGACACCACAGCCAGAAGCTATTACATGTGG} \underline{\textbf{TAA}} \texttt{CTCAGAGGATATTTTGCTTCTGGTAGTAA}$ GGAGCACAAAGACGTTTTTGCTTTATTCTGCAAAAGTGAACAAGTTGAAGACTTTTGTATTTTTGACTTTGCTA GTTTGTGCCAGAGTGGAGAGGCCGGTGGATATTTCAAATTTTTTTAGTATAGCGTATCGCAAGGGTTTGACAC GGCTGCCAGCGACTCTAGGCTTCCAGTCTGTGTTTTGGTTTTTATCTTATCATTATTATGATTGTTATTATATATT ATTATTTTATTTTAGTTGTTGTTGTTGTCTAACTCAATAATGCTGTTCTAACTACAGTGCTCAATAAAATGATTAATG AAAA

Page 305 of 359

192/246

FIGURE 190

MARMSFVIAACO, ULGLIMTSLTESS IONSECPOLCUCEIR PWFTPOSTYREATTVOCHOLLERT PSNLSSDT
OVLLIGSNIKATVOELOO, HUNTELDFSONDTHIRE VEGIALINCTLITHE JEERQ ITEMTEVICLOID, SIN, DEL
YININDISTISAHR PRGLKNLLEH HILSNELBVI DERWEDSTPNLET HIM GENPVIGTIDMTKEPLANTESI UL
AGMYLTITISAAN LOGIDALSES, SFYDMKIVKYPOLALOKUPVIKET DLINNET HIK JOEGD KRINLIKLELE LINI
MCELVSUDRYALDALIPST KREATNIN PRLSYTHRLAF RSVPALBSLMILNINAANAT YQKTVESLIPHLEBI SI HIS
NERLOZU HIRINSKTRIK REMED LSMFCAMBPEYSKHOVKEVULODS SEQCLUH SIRDSP PRINLINDIGTTY
LOCRAMAE PEPET YWYFI CRIKITVET LSDKYKLSSEGTLE ISNIOIED SIGNTUVA ON YQAD TRVATIKVIG
TILDGTOJUKLYVYOTGESISIUVSKWINSIWYSINLIN SIKKE DIPHITTAR VEVPOVIENTIHTH, DEPOTENT
EVILTYSNI HOOT OKSCUNVITENAAFAVDISOCETTALAAVMGSMFAVISLASIAVYFAKFKRKNYHBSLK
KYMKYTSSI PINLELYPPLIKHENGEGSEKKOKOSADTKFTOYDVISSYYMM

Important features: Signal peptide:

WO0268268 [He://E-/W/00206286 opc]

Amino acids 1-25

Transmembrane domain:

Amino acids 508-530

N-glycosylation sites:

Amino acids 69-73;96-100;106-110;117-121;385-389;517-521;582-586;611-615

Tyrosine kinase phosphorylation site:

Amino acids 573-582

N-myristoylation sites:

Amino acids 16-22;224-230;464-470;637-643;698-704

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 306 of 359

193/246

FIGURE 191

GGGAGAGAGATAAATAGCAGCGTGGCTTCCCTGGCTCCTCTCTGCATCCTTCCCGACCTTC CCAGCAATATGCACGTCTGGTCGGCTCCTGCTCCTCTTCTGCTACTGGGGGCC CTGTCTGGATGGCCGCCAGCGATGACCCCATTGAGAAGGTCATTGAAGGGATCAACCGAGG GCTGAGCAATGCAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGGAATCACGC ATGCCGGAAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAGCCACACCGGC AAGGAGTTGGACAAAGGCGTCCAGGGGCTCAACCACGGCATGGACAAGGTTGCCCATGAGAT CAACCATGGTATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCATGGGGTCAACAACG CTGCTGGACAGGCCGGGAAGGAAGCAGACAAAGCGGTCCAAGGGTTCCACACTGGGGTCCAC CAGGCTGGGAAGGAAGCAGAAACTTGGCCAAGGGGTCAACCATGCTGCTGACCAGGCTGG AAAGGAAGTGGAGAAGCTTGGCCAAGGTGCCCACCATGCTGGCCAGGCCGGGAAGGAGC TGCAGAATGCTCATAATGGGGTCAACCAAGCCAGCAAGGAGGCCAACCAGCTGCTGAATGGC AACCATCAAAGCGGATCTTCCAGCCATCAAGGAGGGGCCACAACCACGCCGTTAGCCTCTGG GGCCTCAGTCAACACGCCTTTCATCAACCTTCCCGCCCTGTGGAGGAGCGTCGCCAACATCA TGCCCTAAACTGGCATCCGGCCTTGCTGGGAGAATAATGTCGCCGTTGTCACATCAGCTGAC ATGACCTGGAGGGGTTGGGGGGGGACAGGTTTCTGAAATCCCTGAAGGGGGTTGTACTG GGATTTGTGAATAAACTTGATACACCA

Page 307 of 359

194/246

FIGURE 192

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA66675
><subunit 1 of 1, 247 aa, 1 stop
><mW: 25335, pI: 7.500, NX(s/T): 0
MHLARLVGSCSLLLLLGALSGWAASDDP1EKVIEGINRGLSNAEREVGKALDGINSGITHAG
REVEKVFNGLSNMGSHTGKELDKGVQGLNHGMDKVAHEINHGIGQAGKEAEKLGHGVNNAAG
QAGKEADKAVQGFHTGVHQAGKEAEKLGQGVNHAADQAGKEVEKLGQGAHHAAGQAGKELQN
ANHGVNOASKEANDLINGHOSGSSTBHOGGATTFILASGASVNTFTINIPALMRSVNNINP

Important features of the protein: Signal peptide: amino acids 1-25

WCG268268 [IB#7/E-AV-06206236 opc.]

Homologous region to circumsporozoite (CS) repeats: amino acids 35-225

Page 308 of 359

PCT/US01/21066

WC0268268 [Be://E-W/00206286 opc]

WO 02/08288

195/246

FIGURE 193

Page 309 of 359

196/246

FIGURE 194

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA67300 ><subunit 1 of 1, 172 aa, 1 stop ><ww: 19206, pi: 5.36, NX(s/T): 1 METRPRIGATCLIGFSFILLVISSDGHNGLGKGFGDHIHWRTLEDGKKEAAASGLPLMVI IHKSWCGACKALKPKFAESTEISELSHNFVMVNLEDEEEPKDEDFSPDGGYIPRILFLDP SGKVHPEIINEMGNPSYKYFYVSAEQVVQGMKEAQGRITGDAFRKKHLEDEL

Important features of the protein: Signal peptide:
Amino acids 1-23

Thioredoxin family proteins:

Amino acids 58-75

WCG268268 [Re://E/W/06266286 opc]

N-myristoylation sites: Amino acids 29-35;67-73;150-156

Amidation site: Amino acid 45-49

Page 310 of 359

WCG268268 (IB#7/E-AVO6206286 opc.)

WO 02/08288 PCT/US01/21066

197/246

FIGURE 195

CGGCTCGAGTGCAGCTGTGGGGAGATTTCAGTGCATTGCCTCCCCTGGGTGCTCTTCATCTTGGATTTGAAAGT ACTTGAATGTTTCCCCGCCTGAGCTAACAGTCCATGTGGGTGATTCAGCTCTGATGGGATGTGTTTTCCAGAGC ACAGAAGACAAATGTATATTCAAGATAGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCT ATACTATTACTCCAATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGGGACATCTTAT GCAATGATGGCTCTCCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGAACCTATATCTGTGAAATCCGCCTC AAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTACTGCATGTGCTTCCAGAGGAGCCCAAAGAGCTCATGGT $\tt CCATGTGGGTGGATTGATTCAGATGGGATGTGTTTTCCAGAGCACAGAAGTGAAACACGTGACCAAGGTAGAAT$ GGATATTTTCAGGACGGCGCGCAAAGGAGGAGATTGTATTTCGTTACTACCACAAACTCAGGATGTCTGTGGAG TACTCCCAGAGCTGGGGCCACTTCCAGAATCGTGTGAACCTGGTGGGGGGACATTTTCCGCAATGACGGTTCCAT CATGCTTCAAGGAGTGAGGGAGTCAGATGGAGGAAACTACACCTGCAGTATCCACCTAGGGAACCTGGTGTTCA AGAAAACCATTGTGCTGCATGTCAGCCCGGAAGAGCCTCGAACACTGGTGACCCCGGCAGCCCTGAGGCCTCTG GTCTTGGGTGGTAATCAGTTGGTGATCATTGTGGGAATTGTCTGTGCCACAATCCTGCTCCCTGTTCTGAT ATTGAT CGTGAAGAAGACCT GT GGAAATAAGAGT TCAGTGAATTCTACAGTCTT GGTGAAGAACACGAAGAAGA CTAATCCAGAGATAAAAGAAAAACCCTGCCATTTTGAAAGATGTGAAGGGGAGAAACACATTTACTCCCCAATA ATTGTACGGGAGGTGATCGAGGAAGAAGAACCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCACCCAGT TTGGCCTTCTCTGAGGTCAGATCGGAACAACTCACTTGAAAAAAAGTCAGGTGGGGGAATGCCAAAAACACAGC CACTCTACCAGTGATTTCAGACTCCCGCTCTCCCAGCTGTCCTCCTGTCTCATTGTTTGGTCAATACACTGAAG ATGGAGAATTTGGAGCCTGGCAGAGAGACTGGACAGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATG GACTTGGCCTCTGGAGTGGGACACTGGCCCTGGGAACCAGCTGAGCTGAGTGGCCTCAAACCCCCCGTTGGAT WCG268268 [Her//E/W/QG206236 opc]

WO 02/08288

PCT/US01/21066

Page 311 of 359

198/246

FIGURE 196

MCCPIKLILLEVILDY SIGINDLIN'S PPELTVHYCRSALMGCVPGSTEDKCI FKIDMTIS PGEBARDEVIL'YY SKISDY DIERFONKUHEMGDILCHOSSLLLODDGEADCHT I CELERKERSGYPKEKAVUHLUP PEREKEMYHUP GLIOMGCVPGSTEVKRVYKVEMI FSGRRAKERI VFRYYFKIRRSVEY SGEWGHPONFVALVGDI FRINGSILLIQ GVRESDGGNYTCSIHLGUNVEKTIVIRN'S PEPERTUNYPARKIRPINGFONGUNI VIGITVART HILDSVILLIQ KKTCGNKSSVNSTVLVKNYKKTNPEIKEKPCHPERCEGEKHIYSPIIVREVIEBEBPSEKSEATYMTHEPVBPS LESDRINSLEKKSGGGMPROTOOAF

Page 312 of 359

WC0268268 [He://E-W/00206286 opc]

199/246 FIGURE 197

Page 313 of 359

200/246

FIGURE 198

></usr/scqdb2/sst/DNA/Dnaseqs.min/ss.DNA71269
><subunit 1 of 1, 220 aa, 1 stop
><mw: 24075, pi: 7.67, Nx(s/T): 3
MAGLSRGSARALLAALLASTLLALLVSPARGRGRDHGDWDEASRLPFLPFREDAARVAR
FYTHYSDMGALATISTLEAVRGRFFADULSLBGBGPGAGSGVPYFYLSFLQLSVSNLQZN
PYATLIMTLAQTNFCKKHGFDPGSPLCVHIMLSGTVTKVNBTEMDIAKHSLFIRHFEMKT
WPSSHNWFRAKLNITNIWLDYFGGFKUTYFEEYSHVYTOO

Important features of the protein: Transmembrane domain:

Amino acids 11-29

WC0268268 [Be://E-W/00206286 opc]

N-glycosylation sites: Amino acids

160-164;193-197;216-220

N-myristoylation sites:

Amino acids 3-9;7-13;69-75;97-103

Page 314 of 359

WO0268268 [He://E-/W/00206286 opc]

201/246

FIGURE 199

TCGCCATGGCCGGAATGCAGATCCTGGGAGTCGTCCTGACACTGCTGGGCTGGGTG AATGGCCTGGTCTCCTGTGCCCTGCCCATGTGGAAGGTGACCGCTTTCATCGGCAACAGCAT CGTGGTGGCCCAGGTGTGGGGGGGCCTGTGGATGTCCTGCGTGCAGAGCACCGGCC AGATGCAGTGCAAGGTGTACGACTCACTGCTGGCGCTGCCACAGGACCTGCAGGCTGCACGT GCCCTCTGTGTCATCGCCCTCCTTGTGGCCCTGTTCGGCTTGCTGGTCTACCTTGCTGGGGC CAAGTGTACCACCTGTGTGGAGGAGAAGGATTCCAAGGCCCGCCTGGTGCTCACCTCTGGGA TTGTCTTTGTCATCTCAGGGGTCCTGACGCTAATCCCCGTGTGCTGGACGGCGCATGCCATC ATCCGGGACTTCTATAACCCCCTGGTGGCTGAGGCCCAAAAGCGGGAGCTGGGGGCCTCCCT GCCCCTCGGGGGGTCCCAGGCCCCAGCCATTACATGGCCCGCTACTCAACATCTGCCCCT GCCATCTCTCGGGGGCCCTCTGAGTACCCTACCAAGAATTACGTCTGACGTGGAGGGGAATG GGGGCTCCGCTGGCGCTAGAGCCATCCAGAAGTGGCAGTGCCCAACAGCTTTGGGATGGGTT CGTACCTTTTGTTTCTGCCTCCTGCTATTTTTCTTTTGACTGAGGATATTTAAAATTCATTT GAAAACTGAGCCAAGGTGTTGACTCAGACTCTCACTTAGGCTCTGCTGTTTCTCACCCTTGG ATGATGGAGCCAAAGAGGGGATGCTTTGAGATTCTGGATCTTGACATGCCCATCTTAGAAGC TGTCCCCAAGAGTTCCTGCTGCTGCTGGGGGCTGGGCTTCCCTAGATGTCACTGGACAGCTG CCCCCATCCTACTCAGGTCTCTGGAGCTCCTCTCTCACCCCTGGAAAAACAAATCATCTG TTAACAAAGGACTGCCCACCTCCGGAACTTCTGACCTCTGTTTCCTCCGTCCTGATAAGACG TCCACCCCCAGGGCCAGGTCCCAGCTATGTAGACCCCCGCCCCCACCTCCAACACTGCACC CTTCTGCCCTGCCCCCTCTCTCACCCCCTTTACACTCACATTTTTATCAAATAAAGCATG TTTTGTTAGTGCA

WC0008068 (Ne. // E. N. O0206236 opc.) Page 316 of 359

WO 02/08288 PCT/US01/21066

202/246

FIGURE 200

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA73736
><subunit 1 of 1, 220 aa, 1 stop
><m: 23292, pt: 8.43, NX (s/T): 0
MASAGWQILGVVLTLLGWVNGLVSCALPMWKVTAFIGNSIVVAQVVWEGLWMSCVVQSTQM
QCKVYDSLLALPQDLQAARALCVIALLVALFGLLVYLAGAKCTTCVEKDSKARLVLITSGIV
FYISGVILII PVCWTHAHIIRDFYNDFVAEAQKRELGASLYLGWAASGLLLLGGGLLCCTCP

Transmembrane domains:

SGGSQGPSHYMARYSTSAPAISRGPSEYPTKNYV

amino acids 8-30 (type II), 82-102, 121-140, 166-186

Page 316 of 359

PCT/US01/21066

WC0268268 [Be://E-W/00206286 epc]

WO 02/08288

203/246

FIGURE 201

Page 317 of 359

204/246

FIGURE 202

 ${\tt MKITGGLLLLCTVVYFCSSSEAASLSPKKVDCSIYKKYPVVAIPCPITYLPVCGSDYITYGNECHLCTESLKSNGRVQFLHDGSC}$

Important features: Signal peptide: amino acids 1-19

WCG208268 [He://E./W/00206286 opc]

WC0268268 [He://E-W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 318 of 359

205/246

FIGURE 203

CTCTCGTCGCTTGCGCCTCTCTTCTAGAGCCGAGGGACCCGGTGGCCTCGTCGCTCAGCCCCTATTTCGG TGCTGGAGGGGACCTGCACCCCGGTGCAGCTGGTCGCCCTCATTCGCCACGGCACCCCCTACCCCACGGTCAAA CAGATCCGCAAGCTGAGGCAGCTGCACGGGTTGCTGCAGGCCCGCGGGTCCAGGGATGGCGGGGCTAGTAGTAC TAGAGAAGGGACGCAGGATATCCGACAGCTGCCTGCGTCTGGCCTCGCTCTTCCCGGCCCTTTTCAGCCGT GAGAACTACGGCCGCCTGCGGCTCATCACCAGTTCCAAGCACCGCTGCATGGATAGCAGCGCCGCCTTCCTGCA GGGCTGTGGCAGCACTACCACCTGGCTTGCCGCCGGCACGTCGCAGATATGGAGTTTGGACCTCCAACAG TTAATGATAAACTAATGAGATTTTTTGATCACTGTGAGAAGTTTTTAACTGAAGTAGAAAAAAATGCTACAGCT CTTTATCACGTGGAAGCCTTCAAAACTGGACCAGAAATGCAGAACATTTTAAAAAAAGTTGCAGCTACTTTGCA AGTGCCAGTAAATGATTTAAATGCAGATTTAATTCAAGTAGCCTTTTTCACCTGTTCATTTGACCTGGCAATTA AAGGT GTTAAATCTCCTTGGTGTGATGTTTTTGACATAGATGCTAAAGGTATTAGAATATTTAAATGATCTG AAACAATATTGGAAAAGAGGATATGGGTATACTATTAACAGTCGATCCAGCTGCACCTTGTTTCAGGATATCTT TCAGCACTTGGACAAAGCAGTTGAACAGAAACAAAGGTCTCAGCCAATTTCTTCTCCAGTCATCCTCCAGTTTG GTCATGCAGAGACTCTTCTTCCACTGCTTTCTCTCATGGGCTACTTCAAAGACAAGGAACCCCTAACAGCGTAC AATTACAAAAAACAAATGCATCGGAAGTTCCGAAGTGGTCTCATTGTACCTTATGCCTCGAACCTGATATTTGT GCTTTACCACTGTGAAAATGCTAAGACTCCTAAAGAACAATTCCGAGTGCAGATGTTATTAAATGAAAAGGTGT TACCTTTGGCTTACTCACAAGAAACTGTTTCATTTTATGAAGATCTGAAGAACCACTACAAGGACATCCTTCAG AGTTGTCAAACCAGTGAAGAATGTGAATTAGCAAGGGCTAACAGTACATCTGATGAACTATGAGTAACTGAAGA GAAGCTTTTATATTACTTGAGTATTTCTGTCTTTTCACAGAAAAACATTGGGTTTCTCTCTGGGTTTTGGACATG AAATGTAAGAAAGATTTTTCACTGGAGCAGCTCTCTTAAGGAGAAACAAATCTATTTAGAGAAACAGCTGGCC CTGCAAATGTTTACAGAAATGAAATTCTTCCTACTTATATAAGAAATCTCACACTGAGATAGAATTGTGATTTC GGAACTTTACAGATTGTTCTGCAGTTCTCTCTTTTTCCTCAGGTAGGACAGCTCTAGCATTTTCTTAATCAG GAATATTGTGGTAAGCTGGGAGTATCACTCTGGAAGAAGTAACATCTCCAGATGAGAATTTGAAACAAGAAAC AGAGT GTT GT AAAAGGACACCTT CACTGAAGCAAGT CGGAAAGT ACAATGAAAAT AAATATTTTT GGT ATTT AT TTATGAAATATTTGAACATTTTTCAATAATTCCTTTTTACTTCTAGGAAGTCTCAAAAGACCATCTTAAATTA TTATATGTTTGGACAATTAGCAACAAGTCAGATAGTTAGAATCGAAGTTTTTCAAATCCATTGCTTAGCTAACT TTTTCATTCTGTCACTTGGCTTCGATTTTTATATTTTCCTATTATATGAAATGTATCTTTTGGTTGTTTGATTT TTCTTTCTTTCTTGTAAATAGTTCTGAGTTCTGTCAAATGCCGTGAAAGTATTTGCTATAATAAAGAAAATTC TTGTGACTTTAAAAAAAAA

Page 319 of 359

PCT/US01/21066

206/246 FIGURE 204

MLRARGCLLETSVAPAAALAAALLSSLARGSLLEPRDPVASSLSPYFGTKTRYEDVNPVLLGGEAFWRDFELL EGTCTPVQLVALIRHGTRYPTVKQIRKLKQLHGLLQARGSRDGGASSTGSRDLGAALAWPLMYADNWDGGLVE KORQDMCQLALKLASLFPALFGRENYGRALITSSKHRCWDSSAAFLQGLWGHVHGGLPFDVADWEFGPTVD DLKHRFPDHCEKFLITSVEKNATALHTWAFKTGFEMGNILKKVAATLQVPVNDLNADLIQVAFFTCSFDLAIKG VKSPRCVPEVD DDAKVLEYLNDLKQYWKRGYGYTINSRSGTLFQD1FQHLDWAYEQKGRGGPTSSPV1LQFGH AFTLIFLISHAGYFKOKBPLTAYNYKKQMHRKFRSGLIYPYASNLIFVLYHCENAKTPKEGFRVQMLLNEKVLP LAYSQETVSFFDELNKHYKUTJQSGTSBECELARANTSTGBL

Important features: Signal sequence amino acids 1-30

WO 02/08288

WC0268268 [Be://E-W/00206286 opc]

N-glycosylation sites. amino acids 242-246, 481-485

N-myristoylation sites. amino acids 107-113, 113-119, 117-123, 118-124, 128-134

Endoplasmic reticulum targeting sequence. amino acids 484-489

Page 380 of 359

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288 PCT/US01/21066

207/246

FIGURE 205

GTCCCGGCGCGCGGGCTGGTGTTGTCTCGTGCTCTGGCTCCCGCGTGCGTCGCGCCCA CGGCTTCCGTATCCATGATTATTTGTACTTTCAAGTGCTGAGTCCTGGGGACATTCGATACA TCTTCACAGCCACACCTGCCAAGGACTTTGGTGGTATCTTTCACACAAGGTATGAGCAGATT CACCTTGTCCCCGCTGAACCTCCAGAGGCCTGCGGGGAACTCAGCAACGGTTTCTTCATCCA AGGAGCACGGCGGCGGCGGTGATCATCTCTGACAACGCAGTTGACAATGACAGCTTCTAC GTGGAGATGATCCAGGACAGTACCCAGCGCACAGCTGACATCCCCGCCCTCTTCCTGCTCGG CCGAGACGCTACATGATCCGCCGCTCTCTGGAACAGCATGGGCTGCCATGGGCCATCATTT CCATCCCAGTCAATGTCACCAGCATCCCCACCTTTGAGCTGCTGCAACCGCCCTGGACCTTC TGGTAGAAGAGTTTGTCCCACATTCCAGCCATAAGTGACTCTGAGCTGGGAAGGGGAAACCC AGGAATTTTGCTACTTGGAATTTGGAGATAGCATCTGGGGACAAGTGGAGCCAGGTAGAGGA AAAGGGTTTGGGCGTTGCTAGGCTGAAAGGGAAGCCACACCACTGGCCTTCCCTTCCCCAGG GCCCCAAGGGTGTCTCATGCTACAAGAAGAGGCCAAGACAGGCCCCAGGGCTTCTGGCTA GAACCCGAAACAAAAGGAGCTGAAGGCAGGTGGCCTGAGAGCCATCTGTGACCTGTCACACT CACCTGGCTCCAGCCTCCCCTACCCAGGGTCTCTGCACAGTGACCTTCACAGCAGTTGTTGG AGTGGTTTAAAGAGCTGGTGTTTGGGGACTCAATAAACCCTCACTGACTTTTTAGCAATAAA

208/246

FIGURE 206

Page 321 of 359

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA76532 ><subunit 1 of 1, 188 aa, 1 stop ><MW: 21042, pI: 5.36, NX(S/T): 2

MVPGAAGWCCLVLWLPACVAAHGFRIHDYLYFQVLSPGDIRYIFTATPAKDFGGIFHTRYEQ IHLVPAEPPEACGELSNGFFIQDQIALVERGGCSFLSKTRVVQEHGGRAVIISDNAVDNDSF YVEMIQDSTQRTADIPALFLLGRDGYMIRRSLEQHGLPWAIISIPVNVTSIPTFELLQPPWTFW

Signal peptide:

WCG268268 [He://E./W/06266286 opc]

amino acids 1-20

WC0268268 [Be://E-W/00206286 epc]

WO 02/08288 PCT/US01/21066

Page 322 of 359

209/246

FIGURE 207

Page 323 of 359

210/246

FIGURE 208

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA76541
><subunit 1 of 1, 178 aa, 1 stop
><www: 19600, pi: 5.89, NX(s/T): 1
MHRPEAMLLLITIALLGOFTWAGKMYGPEGGKYFSTTEDYDHEITGLRVSVGLLLVKSVQVK
LGDSWDVKLGALGGNTQEVTLQPGEYITKVFVAFQAFLGMVMYTSKDRYFYFGKLDGQISS
AYPSQEGQVLVGIYGQYQLLGIKSIGFEWNYPLEPFTTEPPVNLTYSANSPVGR

Signal peptide:

WCG268268 [He://E./WOG266286 opc]

amino acids 1-22

Page 324 of 359

PCT/US01/21066

211/246

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288

FIGURE 209

GCCACAGCCACTGGGCCCGAAGTTGCTCAGCCTGAAGTAGACACCACCCTGGGTCGTGTGCGAGGCCGGCAGGT GGGCGT GAAGGGCACAGACCGCCTTGTGAATGTCTTTCTGGGCATTCCATTTGCCCAGCCGCCACTGGGCCCTG ACCGGTTCTCAGCCCCACACCCAGCACAGCCCTGGGAGGGTGTGCGGGATGCCAGCACTGCGCCCCCAATGTGC CTACAAGACGTGGAGACATGAACAGCAGCAGATTTGTCCTCAACGGAAAACAGCAGATCTTCTCCGTTTCAGA GGACT GCCTGGTCCTCAACGTCTATAGCCCAGCTGAGGTCCCCGCAGGGTCCGGTAGGCCGGTCATGGTATGGG TCCATGGAGGCGCTCTGATAACTGGCGCTGCCACCTCCTACGATGGATCAGCTCTGGCTGCCTATGGGGATGTG GT CGT GGTTACAGTCCAGTACCGCCTTGGGGTCCTTGGCTTCTTCAGCACTGGAGATGAGCATGCACCTGGCAA CCAGGGCTTCCTAGATGTGGTAGCTGCTTTGCGCTGGGTGCAAGAAACATCGCCCCCTTCGGGGGTGACCTCA ACTGTGTCACTGTCTTTGGTGGATCTGCCGGTGGGAGCATCATCTCTGGCCTGGTCCTGTCCCCAGTGGCTGCA GGGCTGTTCCACAGAGCCATCACACAGAGTGGGGTCATCACCACCCCAGGGATCATCGACTCTCACCCTTGGCC CCTAGCT CAGAAAATCGCAAACACCTTGGCCTGCAGCTCCAGCTCCCCGGCTGAGATGCTGCAGTGCCTTCAGC GTCTTCCCCAAAAGCCCCAAGGAACTCCTGAAGGAGAAGCCCTTCCACTCTGTGCCCTTCCTCATGGGTGTCAA CAACCATGAGTTCAGCTGGCTCATCCCCAGGGGCTGGGGTCTCCTGGATACAATGGAGCAGATGAGCCGGGAGG ACATGCTGGCCATCTCAACACCCGTCTTGACCAGTCTGGATGTGCCCCCTGAGATGATGCCCACCGTCATAGAT GAATACCTAGGAAGCAACTCGGACGCACAAGCCAAATGCCAGGCGTTCCAGGAATTCATGGGTGACGTATTCAT CAATGTTCCCACCGTCAGTTTTTCAAGATACCTTCGAGATTCTGGAAGCCCTGTCTTTTCTATGAGTTCCAGC ATCGACCCAGTTCTTTTGCGAAGATCAAACCTGCCTGGGTGAAGGCTGATCATGGGGCCGAGGGTGCTTTTGTG TTCGGAGGTCCCTTCCTCATGGACGAGAGCTCCCGCCTGGCCTTTCCAGAGGCCACAGAGGAGGAGGAGCAGCT AAGCCTCACCATGATGGCCCAGTGGACCCACTTTGCCCGGACAGGGGACCCCAATAGCAAGGCTCTGCCTCCTT GGCCCCAATTCAACCAGGCGGAACAATATCTGGAGATCAACCCAGTGCCACGGGCCGGACAGAAGTTCAGGGAG GCCTGGATGCAGTTCTGGTCAGAGACGCTCCCCAGCAAGATACAACAGTGGCACCAGAAGCAGAAGAACAGGAA GGCCCAGGAGGACCTCTGAGGCCAGGCCTGAACCTTCTTGGCTGGGGCAAACCACTCTTCAAGTGGTGGCAGAG GTGACTGGAGTTAT GCTCTTTTGAAATGTCACAAGGCCGCCTCCCACCTCTGGGGCATTGTACAAGTTCTTCCC TCTCCCTGAAGTGCCTTTCCTGCTTTCTTCGTGGTAGGTTCTAGCACATTCCTCTAGCTTCCTGGAGGACTCAC TCCCCAGGAAGCCTTCCCTGCCTTCTCTGGGCTGTGCGGCCCCGAGTCTGCGTCCATTAGAGCACAGTCCACCC GAGGCTAGCACCGTGTCTGTGTCTGTCTCCCCCTCAGAGGAGCTCTCTCAAAATGGGGATTAGCCTAACCCCAC ATAT GGGAATGCCAGCTGCTGAACTTGAACCCAGAGCCTTCAGGTGCCAAAGCCATACTCAGGCCCCCACCGAC ATTGTCCACCCTGGCCAGAAGGGTGCATGCCAATGGCAGACACCTGGGAGAAGTCCTGGGGCGCCAGGG TGCCCAGTCCTGCCCCTGCACAAGACAACAGAATCCATCAGGGCCATGAGTGTCACCCAGACCTGACCCTCAC TGAAAAGCACCAAGAGGTTTTCAGATGGAAGTGAGAGGTGACAGTGTGCTGGCAGCCCTCACAGCCCTCGCTTG TCTCGCTGGGCCTTAGCTGCCTCCCGGGGGCAGGGCTCGGGACCTGCAGCCCTCCATGCCTGACCCTCCCCC CACCCCCGTGGGCTCCTGTGCGGCCGGAGCCTCCCCAAGGAGCGCCCCCCTGCTCCACAGCGCCCAGTCCC GCTGGATCCACTGGGTGAAGCCAGCTGGGCTCCTGAGTCTGGTGGGGACTTTGGAGAACCTTTATGTCTAGCTAA GGGATT GTAAATACACCGATGGGCACTCTGTATCTAGCTCAAGGTTTGTAAACACACCAATCAGCACCCTGTGT CTAGCTCAGTGTTTGTGAATGCACCAATCCACACTCTGTATCTGGCTACTCTGGTGGGGACTTGGAGAACCTTT GTGTCCACACTCTGTATCTAGCTAATCTAGTGGGGATGTGGAGAACCTTTGTGTCTAGCTCAGGGATCGTAAAC GGCGAGACAAGAGAATAAAAGCAGGCTGCCTGAGCCAGCAGTGACAACCCCCCTCGGGTCCCCTCCCACGCCGT GGAAGCTTTGTTCTTTCGCTCTTTGCAATAAATCTTGCTACTGCCCAAAA

Page 385 of 359

212/246

FIGURE 210

MERAVRYESGYLVGVVCLLLACEATATCPEVAQEEVDTTLGRVRGGQVGVKCTDELVNVFLGIFFAQPPLGPDR
FSAPHPAQFMEGVTDASTAFPMCLQVESMISSFYLNGKQG JESVSEDCLLAVYS SPAEVPAGSGRPVMVVH
GGALITGARTSYDGSALAAYGDVVVTVCYRLGVLGFFSTGDERAPGNGGFLDVVAALRHVQENIAFPGGDLMC
VTVFGGSAGGSI ISGUVLSVYAAGLFHRATJGSCVTTFGI ISBHEPLAQKIANTLAGSSSSPAEVMCLQGC
EGEBLVLSKKLKNTI YFLTVDGTVEPKSPKELLKEKPFHSVPFLMGVNNHEPSMLIPRGGGLLDTMEMSREDM
LAISTPYLTSLDVPPEMAGPTVIDEVLGSNSDAGKACGAFOEFMODFTNNFVYSSSTYLROGSGPVFYFEGFR
PSSFAKIKPARVKADHGAEGAFVFGGFFIMDESSRLAFPFATEERKQLSLTMMAQWTHFARTGDPNSKALPPMP
FONQABGYLFRINDVFRAGGFRFRAMMFYSSETLESKIQDHINGQNNRKAGEDD

Important features: Signal peptide: amino acids 1-27

WO0268268 [He://E-/W/00206286 opc]

Transmembrane domain: amino acids 226-245

N-glycosylation site. amino acids 105-109

N-myristoylation sites.

amino acids 10-16, 49-55, 62-68, 86-92, 150-156, 155-161, 162-168, 217-223, 227-233, 228-234, 232-238, 262-268, 357-363, 461-467

Prokaryotic membrane lipoprotein lipid attachment site. amino acids 12-23

Carboxylesterases type-B serine active site. amino acids 216-232

Page 385 of 359

213/246

WC0268268 [like://E_W/06206286 opc.]

FIGURE 211

AACTTCTACATGGGCCTCCTGCTGGTGGTCTTCCTCAGCCTCCTGCCGGTGGCCTACAC CATCATGTCCCTCCCACCCTCTTTGACTGCGGGCCGTTCAGGTGCAGAGTCTCAGTTGCCC GGGAGCACCTCCCCGAGGCAGTCTGCTCAGAGGGCCTCGGCCCAGAATTCCAGTTCTG GTTTCATGCCAGCCTGTAAAAGGCCATGGAACTTTGGGTGAATCACCGATGCCATTTAAGAG GGTTTTCTGCCAGGATGGAAATGTTAGGTCGTTCTGTGTCTGCGCTGTTCATTTCAGTAGCC ATTTTTCTCATTTATTATTTATTTTTAACTGATAGTTGTACATATTTGGGGGTACATGTGA TATTTGGATACATGTATACAATATATAATGATCAAATCAGGGTAACTGGGATATCCATCACA TCAAACATTTATTTTTTTTTTTTTTAGACAGAGTCTCACTCTGTCACCCAGGCTGGAGTGC AGTGGTGCCATCTCAGCTTACTGCAACCTCTGCCTGCCAGGTTCAAGCGATTCTCATGCCTC CACCTCCCAAGTAGCTGGGACTACAGGCATGCACCACAATGCCCAACTAATTTTTGTATTTT TAGTAGAGACGGGGTTTTGCCATGTTGCCCAGGCTGGCCTTGAACTCCTGGCCTCAAACAAT CCACTTGCCTCGGCCTCCCAAAGTGTTATGATTACAGGCGTGAGCCACCGTGCCTGGCCTAA ACATTATCTTTCTTTGTGTTGGGAACTTTGAAATTATACAATGAATTATTGTTAACTGTC CAGTTAACCAACCGTACTTCATCCCCACTCTCTCTATCCTTCCCAACCTCTGATCACCTCA TTCTACTCTACCTCCATGAGATCCACTTTTTTAGCTCCCACATGTGAGTAAGAAAATGCA TTGCTGCAAATGACAGGATTTCGTTCTTAATTTCAATTAAAATAACCACACATGGCAAAAA

WO 02/08288 PC1/US01/21066

Page 327 of 359

214/246

FIGURE 212

MGLLLLVLFLSLLPVAYTIMSLPPSFDCGPFRCRVSVAREHLPSRGSLLRGPRPRIPVLVSC OPVKGHGTLGESPMPFKRVFCODGNVRSFCVCAVHFSSHOPPVAVECLK

Important features of the protein: Signal peptide:

amino acids 1-18

WCG298268 [Ne://E/W/29206286 opc.]

N-myristoylation site. amino acids 86-92

Zinc carboxypeptidases, zinc-binding region 2 signature. amino acids 68-79

Page 328 of 359

WCG268268 (IB#7/E-AV-06206236 opc.)

WO 02/08288 PCT/US01/21066

215/246

FIGURE 213

AGGGCCCGCGGTGGAGAGAGCGACGCCCGAGGGGATGCCGGCGCCCCCCTCT CCAGCTGCAGCTGCAGGAGTTCATCAACGAGCGCGGCGTACTGGCCAGTGGGCGGCCTTGCG AGCCCGGCTGCCGACTTTCTTCCGCGTCTGCCTTAAGCACTTCCAGGCGGTCGTCTCGCCC GGACCCTGCACCTTCGGGACCGTCTCCACGCCGGTATTGGGCACCAACTCCTTCGCTGTCCG GGACGACAGTAGCGGCGGGGGGCGCAACCCTCTCCAACTGCCCTTCAATTTCACCTGGCCGG GTACCTTCTCGCTCATCATCGAAGCTTGGCACGCCCAGGAGACGACCTGCGGCCAGAGGCC TTGCCACCAGATGCACTCATCAGCAAGATCGCCATCCAGGGCTCCCTAGCTGTGGGTCAGAA CTGGTTATTGGATGAGCAAACCAGCACCCTCACAAGGCTGCGCTACTCTTACCGGGTCATCT GCAGTGACAACTACTATGGAGACAACTGCTCCCGCCTGTGCAAGAAGCGCAATGACCACTTC TTGCCAACAGCCTATCTGTCTTTCGGGCTGTCATGAACAGAATGGCTACTGCAGCAAGCCAG CAGAGTGCCTCTGCCGCCCAGGCTGCAGGCCGGCTGTGTAACGAATGCATCCCCCACAAT GGCTGTCGCCACGCACCTGCAGCACTCCCTGGCAATGTACTTGTGATGAGGGCTGGGGAGG CCTGTTTTGTGACCAAGATCTCAACTACTGCACCACCACCCCCATGCAAGAATGGGGGCAA CGTGCTCCAACAGTGGGCAGCGAAGCTACACCTGCACCTGTCGCCCAGGCTACACTGGTGTG GACTGTGAGCTGGAGCTCAGCGAGTGTGACAGCAACCCCTGTCGCAATGGAGGCAGCTGTAA GGACCAGGAGGATGGCTACCACTGCCTGTGTCCTCCGGGCTACTATGGCCTGCACTGTGAAC ACAGCACCTTGAGCTGCGCCGACTCCCCCTGCTTCAATGGGGGCTCCTGCCGGGAGCGCAAC CAGGGGGCCAACTATGCTTGTGAATGTCCCCCCAACTTCACCGGCTCCAACTGCGAGAAGAA AGTGGACAGGTGCACCAGCAACCCCTGTGCCAACGGGGGACAGTGCCTGAACCGAGGTCCAA GCCGCATGTGCCGCTGCCGGCTCCAGGGCACCTACTGTGAACTCCACGTCAGCGAC TGTGCCCGTAACCCTTGCGCCCACGGTGGCACTTGCCATGACCTGGAGAATGGGCTCATGTG CCTCGAGTCCCTGCTTCAACAGGGCCACCTGCTACACCGACCTCTCCACAGACACCTTTGTG TGCAACTGCCCTTATGGCTTTGTGGGCAGCCGCTGCGAGTTCCCCGTGGGCTTGCCGCCCAG CTTCCCCTGGGTGGCCGTCTCGCTGGGTGTGGGGCTGCCAGTGCTGCTGGTACTGCTGGGCA TGGTGGCAGTGGCTGTGCGCAGCTGCGCTTCGACGGCCGGACGACGGCAGCAGGGAAGCC ATGAACAACTTGTCGGACTTCCAGAAGGACAACCTGATTCCTGCCGCCCAGCTTAAAAACAC AAACCAGAAGAAGGAGCTGGAAGTGGACTGTGGCCTGGACAAGTCCAACTGTGGCAAACAGC AAAACCACACTTGGACTATAATCTGGCCCCAGGGCCCCTGGGGCGGGGGACCATGCCAGGA AAGTTTCCCCACAGTGACAAGAGCTTAGGAGAGAGGCGCCACTGCGGTTACACAGTGAAAA GCCAGAGTGTCGGATATCAGCGATATGCTCCCCCAGGGACTCCATGTACCAGTCTGTGTGTT TGATATCAGAGGAGGAATGAATGTGTCATTGCCACGGAGGTATAAGGCAGGAGCCTACCT GGACATCCCTGCTCAGCCCCGCGGCTGGACCTTCCTTCTGCATTGTTTACA

Page 329 of 359

216/246

WCG268268 (IB#7/E-AV-06206236 opc.)

FIGURE 214

MAAASRASGWALLILUALIMQQRAAGSGVPOLOLOEFINERGYLASGRPCEPGCRTFFRVCL
KHPOAVVSPEPCTFGTVSTPYLGTNS FAVRDDSSGGRNEDLOFFNTFWPETFSETSLIEANHA
PGDDLRPEALPPDALISKIAIQGSLAVGONWLLDEQTSTLTRLRYSYRVICSDNYYGDNCSR
LCKKRNDHFGHYVCOPDGNLSCLPGWTGEYCQOPICLSGCHEONGYCSKPAECLCRFGWGGR
CLCRECIPHRGCRHGTCSTPWQCTCDEEWGGLFCDDJDNYCTHBSPCRNGATCSNSGGRSTTC
TCREPGYTGVDCSLELSECDSNPCNGGSCKDOEDGYHCLCPFGYYGLHCEHSTLSCADSFCF
NGGSCRERNOGANYACECPPPHTTSNCEKKVDRCTSNPCANGGQCLNRGPSRRGCRCFFFG
TYCELHVSDCARNPCAHGGTCHDLENGLMCTCPAGFSGRRCEVRTSIDACASSPCFNRATCY
TDLSTDTFVCNCPYGFVGSRCEFFYGLPFSFFWVAYSLGVGLAVLLVLLGWVAVAVRQLRLR
RPDDGSREAMNNLSDFGKDNLIPAAGLKNTNGKKELEVDCGLDKSNCKKQOMHILDVNLAPG
PLGGGTMPGKFPHSDKSLGEKAPLRHSEKPECRISAICSPRDSMYQSVCLISEERNECVIA
TEV

```
Important features of the protein:
Signal peptide:
amino acids 1-26
Transmembrane domain:
amino acids 530-552
N-glycosylation sites.
amino acids 108-112, 183-187, 205-209, 393-397, 570-574, 610-614
Glycosaminoglycan attachment site.
amino acids 96-100
Tyrosine kinase phosphorylation site.
amino acids 340-347
N-myristovlation sites.
amino acids 42-48, 204-210, 258-264, 277-283, 297-303, 383-389,
415-421, 461-467, 522-528, 535-541, 563-569, 599-605, 625-631
Amidation site.
amino acids 471-475
Aspartic acid and asparagine hydroxylation site.
amino acids 339-351
EGF-like domain cysteine pattern signature.
amino acids 173-185, 206-218, 239-251,
                                            270-282, 310-322,
348-360, 388-400, 426-438, 464-476, 506-518
Calcium-binding EGF-like:
amino acids 224-245, 255-276, 295-316, 333-354, 373-394,
```

411-432, 449-470

Page 330 of 359

217/246

WC0268268 [like://E_W/06206286 opc.]

FIGURE 215

CGCGAGGCGCGGGAGCCTGGGACCAGGAGCGAGGCCGCCTACCTGCAGCCGCCCCCACG GCACGGCAGCCACCATGCCCTCCTGCTGCTCCTGCTCCTGTGCGGAGTAGTGGATTTC GCCAGAAGTTTGAGTATCACTACTCCTGAAGAGATGATTGAAAAAGCCAAAGGGGAAACTGC CTATCTGCCATGCAAATTTACGCTTAGTCCCGAAGACCAGGGACCGCTGGACATCGAGTGGC TGATATCACCAGCTGATAATCAGAAGGTGGATCAAGTGATTATTTTATATTCTGGAGACAAA ATTTATGATGACTACTATCCAGATCTGAAAGGCCGAGTACATTTTACGAGTAATGATCTCAA ATCTGGTGATGCATCAATAAATGTAACGAATTTACAACTGTCAGATATTGGCACATATCAGT GCAAAGTGAAAAAGCTCCTGGTGTTGCAAATAAGAAGATTCATCTGGTAGTTCTTGTTAAG CCTTCAGGTGCGAGATGTTACGTTGATGGATCTGAAGAAATTGGAAGTGACTTTAAGATAAA ATGTGAACCAAAAGAAGGTTCACTTCCATTACAGTATGAGTGGCAAAAATTGTCTGACTCAC AGAAAATGCCCACTTCATGGTTAGCAGAAATGACTTCATCTGTTATATCTGTAAAAAAATGCC TCTTCTGAGTACTCTGGGACATACAGCTGTACAGTCAGAAACAGAGTGGGCTCTGATCAGTG CCTGTTGCGTCTAAACGTTGTCCCTCCTTCAAATAAAGCTGGACTAATTGCAGGAGCCATTA TAGGAACTTTGCTTGCTCTAGCGCTCATTGGTCTTATCATCTTTTGCTGTCGTAAAAAGCGC AGAGAAGAAAATATGAAAAGGAAGTTCATCACGATATCAGGGAAGATGTGCCACCTCCAAA GAGCCGTACGTCCACTGCCAGAAGCTACATCGGCAGTAATCATCCCTGGGGTCCATGT CTCCTTCCAACATGGAAGGATATTCCAAGACTCAGTATAACCAAGTACCAAGTGAAGACTTT GAACGCACTCCTCAGAGTCCGACTCTCCCACCTGCTAAGTTCAAGTACCCTTACAAGACTGA TGGAATTACAGTTGTATAAATATGGACTACTGAAGAATCTGAAGTATTGTATTATTTGACTT TATTTTAGGCCTCTAGTAAAGACTTAAATGTTTTTTAAAAAAAGCACAAGGCACAGAGATTA GAGCAGCTGTAAGAACACATCTACTTTATGCAATGGCATTAGACATGTAAGTCAGATGTCAT GTCAAAATTAGTACGAGCCAAATTCTTTGTTAAAAAACCCTATGTATAGTGACACTGATAGT TAAAAGATGTTTTATTATATTTTCAATAACTACCACTAACAAATTTTTAACTTTTCATATGC ATATTCTGATATGTGGTCTTTTAGGAAAAGTATGGTTAATAGTTGATTTTTCAAAGGAAATT TTAAAATTCTTACGTTCTGTTTAATGTTTTTGCTATTTAGTTAAATACATTGAAGGGAAATA CCCGTTCTTTTCCCCTTTTATGCACACACAGAACACGCGTTGTCATGCCTCAAACTATTT TTTATTTGCAACTACATGATTTCACACAATTCTCTTAAACAACGACATAAAATAGATTTCCT TGTATATAAATAACTTACATACGCTCCATAAAGTAAATTCTCAAAGGTGCTAGAACAAATCG TCCACTTCTACAGTGTTCTCGTATCCAACAGAGTTGATGCACAATATATAAATACTCAAGTC CAATATTAAAAACTTAGGCACTTGACTAACTTTAATAAAATTTCTCAAACTATATCAATATC TAAAGTGCATATATTTTTTAAGAAAGATTATTCTCAATAACTTCTATAAAAATAAGTTTGAT GGTTTGGCCCATCTAACTTCACTACTATTAGTAAGAACTTTTAACTTTTAATGTGTAGTAAG GTTTATTCTACCTTTTCTCAACATGACACCAACACAATCAAAAACGAAGTTAGTGAGGTGC TAACATGTGAGGATTAATCCAGTGATTCCGGTCACAATGCATTCCAGGAGGAGGTACCCATG TCACTGGAATTGGGCGATATGGTTTATTTTTTCTTCCCTGATTTGGATAACCAAATGGAACA GGAGGAGGATAGTGATTCTGATGGCCATTCCCTCGATACATTCCTGGCTTTTTTCTGGGCAA AGGGTGCCACATTGGAAGAGGTGGAAATATAAGTTCTGAAATCTGTAGGGAAGAGAACACAT TAAGTTAATTCAAAGGAAAAATCATCATCTATGTTCCAGATTTCTCATTAAAGACAAAGTT ACCCACACACTGAGATCACATCTAAGTGACACTCCTATTGTCAGGTCTAAATACATTAAAA ACCTCATGTGTAATAGGCGTATAATGTATAACAGGTGACCAATGTTTTCTGAATGCATAAAG AAATGAATAAACTCAAACACAGTACTTCCTAAACAACTTCAACCAAAAAAGACCAAAACATG GAACGAATGGAAGCTTGTAAGGACATGCTTGTTTTAGTCCAGTGGTTTCCACAGCTGGCTAA GCCAGGAGTCACTTGGAGGCTTTTAAATACAAAACATTGGAGCTGGAGGCCATTATCCTTAG CAAACTAATGCAGAAACAGAAAATCAACTACCGCATGTTCTCACTTATAAGTGGGAGGTAAT GATAAGAACTTATGAACACAAAGAAGGAAACAATAGACATTGGAGTCTATTTGAGAGGGGAG GGTGGGAGAAGGAAAAGGACAGAAAAGATAACTATTGAGTACTGCCTTCACACCTGGGTGA TGAAATAATATGTACAACAAATCCCTGTGACACATGTTTACCTATGGAACAAACCTTCATGT AAAAAAAAAAAAAAAAAAAAAA

Page 331 of 359

218/246

FIGURE 216

></usr/segdb2/sst/DNA/Dnasegs.full/ss.DNA82361

><subunit 1 of 1, 352 aa, 1 stop

><MW: 38938, pI: 7.86, NX(S/T): 3

MALLLCFVLLCGVVDFARSLSITTPEEMIEKAKGETAYLPCKFTLSPEDOGPLDIEWLISPA DNOKVDOVIILYSGDKIYDDYYPDLKGRVHFTSNDLKSGDASINVTNLOLSDIGTYOCKVKK APGVANKKIHLVVLVKPSGARCYVDGSEEIGSDFKIKCEPKEGSLPLOYEWOKLSDSOKMPT SWLAEMTSSVISVKNASSEYSGTYSCTVRNRVGSDOCLLRLNVVPPSNKAGLIAGAIIGTLL ALALIGLIIFCCRKKRREEKYEKEVHHDIREDVPPPKSRTSTARSYIGSNHSSLGSMSPSNM EGYSKTOYNOVPSEDFERTPOSPTLPPAKFKYPYKTDGITVV

Signal sequence. amino acids 1-19

WO0268268 [He://E-W/00206286 opc]

Transmembrane domain:

amino acids 236-257

N-qlycosylation sites.

amino acids 106-110, 201-205, 298-302

Tyrosine kinase phosphorylation sites.

amino acids 31-39, 78-85, 262-270

N-myristoylation sites.

amino acids 116-122, 208-214, 219-225, 237-243, 241-247, 245-251, 296-302

Myelin P0 protein.

amino acids 96-125

Page 332 of 359

WC0268268 [Be://E-W/00206286 epc]

219/246

FIGURE 217

GATGGCGCAGCCACAGCTTCTGTGAGATTCGATTTCTCCCCAGTTCCCCTGTGGGTCTGAGG GGACCAGAAGGGTGAGCTACGTTGGCTTTCTGGAAGGGGAGGCTATATGCGTCAATTCCCCA GTTCCAGGCCTTACCTGCTGGGCACTAACGGCGGAGCCAGGATGGGGACAGAATAAAGGAGC CACGACCTGTGCCACCAACTCGCACTCAGACTCTGAACTCAGACCTGAAATCTTCTCTTCAC GGGAGGCTTGGCAGTTTTTCTTACTCCTGTGGTCTCCAGATTTCAGGCCTAAGATGAAAGCC TCTAGTCTTGCCTTCAGCCTTCTCTCTGCTGCGTTTTATCTCCTATGGACTCCTTCCACTGG ACTGAAGACACTCAATTTGGGAAGCTGTGTGATCGCCACAAACCTTCAGGAAATACGAAATG GATTTTCTGAGATACGGGGCAGTGTGCAAGCCAAAGATGGAAACATTGACATCAGAATCTTA AGGAGGACTGAGTCTTTGCAAGACACAAAGCCTGCGAATCGATGCTGCCTCCTGCGCCATTT GCTAAGACTCTATCTGGACAGGGTATTTAAAAACTACCAGACCCCTGACCATTATACTCTCC GGAAGATCAGCAGCCTCGCCAATTCCTTTCTTACCATCAAGAAGGACCTCCGGCTCTCTCAT GCCCACATGACATGCCATTGTGGGGAGGAAGCAATGAAGAAATACAGCCAGATTCTGAGTCA CTTTGAAAAGCTGGAACCTCAGGCAGCAGTTGTGAAGGCTTTGGGGGAACTAGACATTCTTC TGCAATGGATGGAGGAGACAGAATAGGAGGAAAGTGATGCTGCTGCTAAGAATATTCGAGGT CAAGAGCTCCAGTCTTCAATACCTGCAGAGGAGGCATGACCCCCAAACCACCATCTCTTTACT GTACTAGTCTTGTGCTGGTCACAGTGTATCTTATTTATGCATTACTTGCTTCCTTGCATGAT TGTCTTTATGCATCCCCAATCTTAATTGAGACCATACTTGTATAAGATTTTTGTAATATCTT ATTTTTTTACTTGGACATGAAACTTTAAAAAAATTCACAGATTATATTTATAACCTGACTAG AGCAGGTGATGTATTTTATACAGTAAAAAAAAAAAACCTTGTAAATTCTAGAAGAGTGGCT AGGGGGGTTATTCATTTGTATTCAACTAAGGACATATTTACTCATGCTGATGCTCTGTGAGA TATTTGAAATTGAACCAATGACTACTTAGGATGGGTTGTGGAATAAGTTTTGATGTGGAATT GCACATCTACCTTACAATTACTGACCATCCCCAGTAGACTCCCCAGTCCCATAATTGTGTAT CTTCCAGCCAGGAATCCTACACGGCCAGCATGTATTTCTACAAATAAAGTTTTCTTTGCATA CCAAAAAAAAAAAAAAAAA

Page 333 of 359

PCT/US01/21066

WCG208268 [He://E./W/00206286 opc]

WO 02/08288

220/246 FIGURE 218

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA83500

MKASSLAFSILISAAFYILMTPSTGLKTINIGSCVIATNIGEIRNGFSEIRGSVQAKDGN IDIRTIRRTESLQDTKPANRCCLIRHLIRLYLDRVFKNYQTPDHYTIRKISSLANSFLT IKKDLRLSHAHNTCHCGERANKKYSQTLSHFEKLEPQAAVVKALGELDILLQWMEETS

Page 334 of 359

WCG268268 (IB#7/E-AVO6206286 opc.)

221/246

FIGURE 219

CGCGGAGCCCTGCGCTGGGAGGTGCACGGTGTGCACGCTGGACTGGACCCCCATGCAACCCC GCGCCCTGCGCCTTAACCAGGACTGCTCCGCGCGCCCCTGAGCCTCGGGCTCCGGCCCGGAC GCTTTAAAAGTGCTACTAGAACAAGAGAAAACGTTTTTCACTCTTTTAGTATTACTAGGCT ATTTGTCATGTAAAGTGACTTGTGAATCAGGAGACTGTAGACAGCAAGAATTCAGGGATCGG TCTGGAAACTGTGTTCCCTGCAACCAGTGTGGGCCAGGCATGGAGTTGTCTAAGGAATGTGG CTTCGGCTATGGGGAGGATGCACAGTGTGTGACGTGCCGGCTGCACAGGTTCAAGGAGGACT GGGGCTTCCAGAATGCAAGCCCTGTCTGGACTGCGCAGTGGTGAACCGCTTTCAGAAGGCA AATTGTTCAGCCACCAGTGATGCCATCTGCGGGGACTGCTTGCCAGGATTTTATAGGAAGAC GAAACTTGTCGGCTTTCAAGACATGGAGTGTGTGCCTTGTGGAGACCCTCCTCCTCCTTACG AACCGCACTGTGCCAGCAAGGTCAACCTCGTGAAGATCGCGTCCACGGCCTCCAGCCCACGG GACACGGCGCTGCCGTTATCTGCAGCGCTCTGGCCACCGTCCTGCTGGCCCTGCTCAT CCTCTGTGTCATCTATTGTAAGAGACAGTTTATGGAGAAGAACCCAGCTGGTCTCTGCGGT CGCAGGACATTCAGTACAACGGCTCTGAGCTGTCGTGTTTTGACAGACCTCAGCTCCACGAA TATGCCCACAGAGCCTGCCAGTGCCGCCGTGACTCAGTGCAGACCTGCGGGCCGGTGCG CTTGCTCCATCCATGTGCTGTGAGGAGGCCTGCAGCCCCAACCCGGCGACTCTTGGTTGTG GGGTGCATTCTGCAGCCAGTCTTCAGGCAAGAACGCAGGCCCAGCCGGGGAGATGGTGCCG ACTTTCTTCGGATCCCTCACGCAGTCCATCTGTGGCGAGTTTTCAGATGCCTGGCCTCTGAT GCAGAATCCCATGGGTGACAACATCTCTTTTTGTGACTCTTATCCTGAACTCACTGGAG AAGACATTCATTCTCTCAATCCAGAACTTGAAAGCTCAACGTCTTTGGATTCAAATAGCAGT CAAGATTTGGTTGGTGGGGCTGTTCCAGTCCAGTCTCATTCTGAAAACTTTACAGCAGCTAC TGAGAAGCCAGCTAGATCAGGAGAGTGGCGCTGTCATCCACCCAGCCACTCAGACGTCCCTC CAGGAAGCTTAAAGAACCTGCTTCTTTCTGCAGTAGAAGCGTGTGCTGGAACCCAAAGAGTA CTCCTTTGTTAGGCTTATGGACTGAGCAGTCTGGACCTTGCATGGCTTCTGGGGCAAAAATA AATCTGAACCAAACTGACGGCATTTGAAGCCTTTCAGCCAGTTGCTTCTGAGCCAGACCAGC TGTAAGCTGAAACCTCAATGAATAACAAGAAAAGACTCCAGGCCGACTCATGATACTCTGCA TCTTTCCTACATGAGAAGCTTCTCTGCCACAAAAGTGACTTCAAAGACTGATGGGTTGAGCT GGCAGCCTATGAGATTGTGGACATATAACAAGAAACAGAAATGCCCTCATGCTTATTTTCAT CATACCGCCTATGAAATATCAGATAAATTACCTTAGCTTTTATGTAGAATGGGTTCAAAAGT GAGTGTTTCTATTTGAGAAGGACACTTTTTCATCATCTAAACTGATTCGCATAGGTGGTTAG AATGGCCCTCATATTGCCTGCCTAAATCTTGGGTTTATTAGATGAAGTTTACTGAATCAGAG GAATCAGACAGAGGAGGATAGCTCTTTCCAGAATCCACACTTCTGACCTCAGCCTCGGTCTC ATGAACACCCGCTGATCTCAGGAGAACACCTGGGCTAGGGAATGTGGTCGAGAAAGGGCAGC CCATTGCCCAGAATTAACACATATTGTAGAGACTTGTATGCAAAGGTTGGCATATTTATATG AAAATTAGTTGCTATAGAAACATTTGTTGCATCTGTCCCTCTGCCTGAGCTTAGAAGGTTAT AGAAAAAGGGTATTTATAAACATAAATGACCTTTTACTTGCATTGTATCTTATACTAAAGGC TTTAGAAATTACAACATATCAGGTTCCCCTACTACTGAAGTAGCCTTCCGTGAGAACACACC ACATGTTAGGACTAGAAGAAAATGCACAATTTGTAGGGGTTTGGATGAAGCAGCTGTAACTG AGTGCTCCATCCCTACCATCTACACATTAGCATTGTCTCTAGAGCTAAGACAGAAATTAAC CCCGTTCAGTCACAAAGCAGGGAATGGTTCATTTACTCTTAATCTTTATGCCCTGGAGAAGA CCTACTTGAACAGGGCATATTTTTTAGACTTCTGAACATCAGTATGTTCGAGGGTACTATGA TATTTTGGTTTGGAATTGCCCTGCCCAAGTCACTGTCTTTTAACTTTAAACTGAATATTAA AATGTATCTGTCTTTCCT

WC0208088 [He WE AV 00208288 opt.] Finger 335 of 256

WO 02/08288 PCT/US01/21066

222/246

FIGURE 220

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA84210
><subunit 1 of 1, 417 aa, 1 stop</pre>

><MW: 45305, pI: 5.12, NX(S/T): 6

MALKVLLEGEKTFTTLLVLIGYLSCKVTCESGDCRQQEFRDRSGNCVPCNQCGPGMELSK ECGFGYGEDAQCVTCRLHRFKEDWGFQKCKPCLDCAVVNRROKANCSATSDAICGBCLPG FYRKTKLVGFQDMECVPCGDPPPPYEPHCASKVNLVKLASTASSPRDTALAAVICSALAT VLLALLILCVIYCKRQFMEKKPSWSLRSQDIQYNGSELSCFDRPQLHEYAHRACCQCRRD SVQTCGPVRLLPSWCCEEACSPNPATLGGGVHSAASLQARNAGPAGEMVPTFFGSLTQSI CGEFSDAWPLWQNPMGGDNISFCDSYPELTGEDIHSLNPELESSTSLDSNSSQDLVGGA PVQSHSENFTAATDLSKYNNTLVESSTQDAITMRSQLDQESGAVIHPATQTSLQBA

Important features of the protein: Signal peptide:

Amino acids

1-25

Transmembrane domain:

Amino acids 169-192

N-glycosylation sites:

Amino acids

105-109;214-218;319-323;350-354;368-372;379-383

cAMP- and cGMP-dependent protein kinase phosphorylation sites: Amino acids

200-204;238-242

Tyrosine kinase phosphorylation site:

Amino acids

N-myristoylation sites:

Amino acids

55-61:215-221:270-276

Prokaryotic membrane lipoprotein lipid attachment site: Amino acids

259-270

TNFR/NGFR family cysteine-rich region proteins:

Amino acids

89-96

Page 336 of 359

WO0268268 [He://E-/W/00206286 opc]

223/246

FIGURE 221

CTAGAGAGTATAGGGCAGAAGGATGGCAGATGAGTGACTCCACATCCAGAGCTGCCTCCCTT TAATCCAGGATCCTGTCCTGTCCTGTAGGAGTGCCTGTTGCCAGTGTGGGGTGAGACA AGTTTGTCCCACAGGGCTGTCTGAGCAGATAAGATTAAGGGCTGGGTCTGTGCTCAATTAAC TCCTGTGGGCACGGGGCTGGGAAGACCAAGTCAGCGGTGCCTACAGTCAGCACCATGCTG GGCCTGCCGTGGAAGGGAGGTCTGTCCTGGGCGCTGCTGCTTCTCTTAGGCTCCCAGAT CCTGCTGATCTATGCCTGGCATTTCCACGAGCAAAGGGACTGTGATGAACACAATGTCATGG TACTATGCCTACAGACTGGGGCACATCTTGAATTCCTGGAAGGAGCAGGTGGAGTCCAAGAC TGTATTCTCAATGGAGCTACTGCTGGGGAGAACTAGGTGTGGGAAATTTGAAGACGACATTG ACAACTGCCATTTCCAAGAAAGCACAGAGCTGAACAATACTTTCACCTGCTTCTTCACCATC AGCACCAGGCCCTGGATGACTCAGTTCAGCCTCCTGAACAAGACCTGCTTGGAGGGATTCCA CTGAGTGAAACCCACTCACAGGCTTGTCCATGTGCTGCTCCCACATTCCGTGGACATCAGCA CATGTGTTTGAGATCTCAGATCAGTGTTTTAGAAAATCCACACATCTTGAGCCTAATCATGT ΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑ

WO 02/08288

224/246

FIGURE 222

Page 337 of 359

PCT/US01/21066

MLGLPWKGGLSWALLLLLLGSQILLIYAWHFHEQRDCDEHNVMARYLPATVEFAVHTFNQQS KDYYAYRLGHILNSWKEQVESKTVFSMELLLGRTRCGKFEDDIDNCHFQESTELNNTFTCFF TISTRFWYYOFSLLNKTCLEGFH

Important features of the protein:
Signal peptide:
amino acids 1-25

N-glycosylation sites. amino acids 117-121, 139-143

N-myristoylation site. amino acids 9-15

Page 338 of 359

225/246

WC0268268 [He://E-W/00206286 opc]

FIGURE 223

WCG268268 [Re://E/W/06266286 opc]

41-185

WO 02/08288 PCT/US01/21066

Page 339 of 359

226/246

FIGURE 224

MVMLLLLLSALAGLFGAAEGQAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPTTFENG RCIQANYSLMENGKIKVLNQELBADGTVNQIFGEATPVNLTEPAKLFVKESWFMPSAPY WILATDYENYALVYSCTCIIQLFHVDFAWILARNPNLPPETVDSLKNILTSNNIDVKKM TVTDQVNCPKLS

```
Signal sequence 1-16
N-glycosylation site.
65-68
98-101
CAMP- and oGMP-dependent protein kinase phosphorylation site.
175-178
N-myristoylation site.
13-18
16-21
Lipccalin proteins.
36-47
120-130
Lipccalin / cytosolic fatty-acid binding proteins
```

Page 340 of 359

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288 PCT/US01/21066

227/246

FIGURE 225

GGGTGATTGAACTAAACCTTCGCCGCACCGAGTTTGCAGTACGGCCGTCACCCGCACCGCTG CCTGCTTGCGGTTGGAGAAATCAAGGCCCTACCGGGCCTCCGTAGTCACCTCTCTATAGTGG GCGTGGCCGAGGCCGGGGTGACCCTGCCGGAGCCTCCGCTGCCAGCGACATGTTCAAGGTAA TTCAGAGGTCCGTGGGGCCAGCCAGCCTGAGCTTGCTCACCTTCAAAGTCTATGCAGCACCA AAAAAGGACTCACCTCCCAAAAATTCCGTGAAGGTTGATGAGCTTTCACTCTACTCAGTTCC TGAGGGTCAATCGAAGTATGTGGAGGAGGCAAGGAGCCAGCTTGAAGAAAGCATCTCACAGC TCCGACACTATTGCGAGCCATACACAACCTGGTGTCAGGAAACGTACTCCCAAACTAAGCCC AAGATGCAAAGTTTGGTTCAATGGGGGTTAGACAGCTATGACTATCTCCAAAATGCACCTCC TGGATTTTTCCGAGACTTGGTGTTATTGGTTTTTGCTGGCCTTATTGGACTCCTTTTGGCTA TATTATCCACAACAAGCCATCGTGTTTGCCCAGGTCAGTGGGGAAGATTATATGACTGGGG TTTACGAGGATATATAGTCATAGAAGATTTGTGGAAGGAGAACTTTCAAAAGCCAGGAAATG TGAAGAATTCACCTGGAACTAAGTAGAAAACTCCATGCTCTGCCATCTTAATCAGTTATAGG TAAACATTGGAAACTCCATAGAATAAATCAGTATTTCTACAGAAAAATGGCATAGAAGTCAG TATTGAATGTATTAAATTGGCTTTCTTCTTCAGGAAAAACTAGACCAGACCTCTGTTATCTT CTGTGAAATCATCCTACAAGCAAACTAACCTGGAATCCCTTCACCTAGAGATAATGTACAAG CCTTAGAACTCCTCATTCTCATGTTGCTATTTATGTACCTAATTAAAACCCAAGTTTAAAAA ΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑΑ

Page 341 of 359

WO 02/08288 PCT/US01/21066

228/246

FIGURE 226

MFKVIQRSVGPASLSLLTFKVYAAPKKDSPPKNSVKVDELSLYSVPEGQSKYVEEARSQLEE SISQLRHYCEPYTTMCQETYSQTKPKMQSLVQWGLDSYDYLQNAPPGFFPRLGVIGFAGLIG LLLARGSKIKKLVYPPGFMGLAASLYYPQQAIVFAQVSGERLYDWGLRGYIVIEDLWKENFQ KPCNVKNSPGTK

Important features:

Signal peptide: Amino acids 1-23

WCG268268 [He://E-/WOG266286 opc]

Transmembrane domain:

Amino acids 111-130

cAMP- and cGMP-dependent protein kinase phosphorylation site: \mbox{Amino} acids $26\mbox{-}30$

Tyrosine kinase phosphorylation site: Amino acids 36-44

N-myristoylation sites:

Amino acids 124-130;144-150;189-195

WC6268368 (Her//E/W/06266286 opc)

WO 02/08288 PCT/US01/21066

Page 342 of 359

229/246

FIGURE 227

ACTGGAGCTGTTCGCGCCTCCCGGCTCCCACCGCAGCCCACCGGCAGAGGAGTCGCTACCA GCGCCCAGTGCGCTCTGTCAGTCCGCAAACTCCTTGCCGCCCCCGGGCTGGGCACCAAA TACCAGGCTACCATGGTCTACAAGACTCTCTTCGCTCTTTGCATCTTAACTGCAGGATGGAG GGTACAGAGTCTGCCTACATCAGCTCCTTTGTCTGTTTCTCTTCCGACAAACATTGTACCAC CGACCACCATCTGGACTAGCTCTCCACAAAACACTGATGCAGACACTGCCTCCCCATCCAAC GGCACTCACAACAACTCGGTGCTCCCAGTTACAGCATCAGCCCCAACATCTCTGCTTCCTAA GAACATTTCCATAGAGTCCAGAGAAGAGGAGATCACCAGCCCAGGTTCGAATTGGGAAGGCA CAAACAGAGCCCTCACCTTCTGGGTTCTCGTCAACAAGCGGTGGAGTCCACTTAACAACC ACGTTGGAGGACACAGCTCGGGCACTCCTGAAGCAGGCGTGGCAGCTACACTGTCGCAGTC CGCTGCTGAGCCTCCCACACTCATCTCCCCTCAAGCTCCAGCCTCATCACCCTCATCCCTAT AGCACCCAACCCACTGGAGCTCCAACTGCACCAGAGTCCCCGACAGAGGAGTCCAGCTCTGA CCACACACCCACTTCACATGCCACAGCTGAGCCAGTGCCCCAGGAGAAACACCCCCAACAA CTGTGTCAGGCAAAGTGATGTGTGAGCTCATAGACATGGAGACCACCACCACCTTTCCCAGG GTGATCATGCAGGAAGTAGAACATGCATTAAGTTCAGGCAGCATCGCCGCCATTACCGTGAC CCTATGGAAGACTTTTGGACGACCATGACTACGGGTCCTGGGGAAACTACAACAACCCTCTG GTGCTTATCCAGTAGAATTAATAAGTACCTGATGCGCATTGAACGACAATCTTAAGCCCTGT TTTGTTGGTATGGTTGTTTTTGTTTTCCTCCCTCTCCTCTGGCTGCTACAACTTCCCCTTTC TGGTACAAGAAGAACCATTCTTTAAAGGTGAGTGGAGGCTGATTTGCAGCTGAAGTGGGCCA GCCTTGCACCAGCCAGACCACCATGGTGAAGGCTTCTTTCCCCACTGCAGGACCCAC TTTCATTTGTGTTATTTCTTAAACTTCTATTTAGGAAATTACATTAAGTATTAATGAGGGGA AAGGAAATGAGCTCTACGAGGATTTCACCTTGCATGGGAGAGAGCAGGGTTTTCTCAGATTC TGGAAAGCAGCTTCTTAGCTGCCTAATTAATGAAAGATGAAAATAGGAAGTGCCCTGGAGGG GGCCAGCAGGTCACGGGGCAGAATCTCTCAGGTTGCTGTGGGATCTCAGTGTGCCCCTACCT GTTCTCCCCTCCAGGCCACCTGTCTCTGTAAAGGATGTCTGCTCTGTTCAAAAGGCAGCTGG GATCCCAGCCCACAGTGATCAGCAGAGTTGCATTTCCAAAGAAAAAGGCTATGAGATGAGC TGAGTTATAGAGAAAGGGAGAGGCATGTACGGTGTGGGGAAGTGGAAGAGAAGCTGGCGG GGGAGAAGGAGCTAACCTGCACTGAGTACTTCATTAGGACAAGTGAGAATCAGCTATTGAT AATGGCCAGAGATATCCACAGCTTGGAGGAGCCCAGAGACTGTTTGCTTTATACCCACAG CAACTGGTCCACTGCTTTACTGTCTGTTGGATAATGGCTGTAAAATGTTTAAAAAC

Page 343 of 359

230/246

FIGURE 228

MVYKTLFALCILTAGWRYQSLPTSAPLSVSLPYNIVPPTTIWTSSPQNTDADTASPSNCTHN NSVLPYTASAPTSLLPKHISIESREEHITSPGSNWEGTNTDBSPGSTSTSGCYHLTTTLEE HSSGTPEAGVAATLSQSAAEPPTLISPQAPASSPSSLSTSPPEVFSASVTTNHSSTVTSTQP TGAPTAPESPTEESSSDHTPTSHATAEPVPQEKTPFTTVSGKVMCELIDMETTTTFFRVIMQ EVEHALSSGSIAAITYVTIAVYLLYFGVAAYLKIRSSYGKLLDDHDYGSWGNYNNFLYDDS

Important features of the protein: Signal peptide:

amino acids 1-20

WCG268268 [Re://E/W/06266286 opc]

Transmembrane domain:

amino acids 258-278

N-glycosylation sites.

amino acids 58-61, 62-65, 80-83, 176-179

Casein kinase II phosphorylation sites. amino acids 49-52, 85-88, 95-98, 100-103, 120-123, 121-124, 141-144, 164-167, 191-194, 195-198, 200-203

Tyrosine kinase phosphorylation site.

amino acids 289-296

N-myristoylation sites.

amino acids 59-64, 115-120, 128-133, 133-138, 257-262, 297-302

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 344 of 359

231/246

FIGURE 229

Page 345 of 359

232/246

FIGURE 230

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA92265

><subunit 1 of 1, 165 aa, 1 stop ><MW: 17786, pI: 8.43, NX(S/T): 0

MMRCCRRRCCRQFPHALRPLLLLPLVLLPPLAAAAAGPNRCDTIYQGFAECLIRLGDSM GRGGELETICRSWNDFHACASQVLSGCPEEAAAVWESLQQEARQAPRFNNLHTLCGAPVH VRBRGTGSETNOETLBATAPALPMAPAPLLAAALALAYJLBPLA

Important features of the protein:

Signal peptide:

WCG208268 [He://E./W/00206286 opc]

Amino acids 1-35

Transmembrane domain:

Amino acids 141-157

N-myristoylation site:

Amino acids 127-133

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 77-88

WO0268268 [He://E-/W/00206286 opc]

WO 02/08288 PCT/US01/21066

Page 346 of 359

233/246

FIGURE 231

Page 347 of 359

234/246

FIGURE 232

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA92274

><subunit 1 of 1, 223 aa, 1 stop ><MW: 25402, pI: 8.14, NX(S/T): 1

MGWTMRLVTAALLIGIMMVVTGDEDENSPCAHEALLDEDTLFCQGLEVFYPELGNIGCKVVP DCNNYRQKTTSWMEFIVKFPGAVDGATYILVMVDPDAPSRAEPRQRFWRHWLVTDIKGADLK KGKIQGQELSAYQAPSPPAHSGFHRYQFFVYLQGGKVISLLPKENKTRGSWKMDRFLNRFHL GEPEASTOFMTONYQDSFTLQAPRGRASEPKHKTROR

Important features of the protein: Signal peptide:

amino acids 1-22

WC0208268 [Her//E_W/00Z06286 opc.]

N-glycosylation site. amino acids 169-173

Tyrosine kinase phosphorylation site. amino acids 59-68

N-myristoylation sites. amino acids 54-60, 83-89, 130-136

Phosphatidylethanolamine signature. amino acids 113-157

235/246

FIGURE 233

WO 02/08288

PCT/US01/21066

Page 349 of 359

236/246

FIGURE 234

></usr/seqdb2/sst/DNA/Dnaseqs.full/ss.DNA92282
><subunit 1 of 1, 177 aa, 1 stop
><MW: 20452, pI: 8.00, NX(S/T): 2</pre>

MKLQCVSLMLLGTLILICSVDNH6LRRCLISTDMHHIEESFQEIKRAIQAKDTFPNVTILST LETLQIIKPLDVCCVTKNLLAFYVDRVFKDHQEPNPKILRKISSIANSFLYMQKTLRQCQEQ RQCHCRQEATNATRVIHDNYDQLEVHAAAIKSLGELDVFLAWINKNHEVMESA

Signal sequence: amino acids 1-18

N-glycosylation sites. amino acids 56-60, 135-139

cAMP- and cGMP-dependent protein kinase phosphorylation site. amino acids $102-106^{\circ}$

N-myristoylation site. amino acids 24-30

Actinin-type actin-binding domain signature 1. amino acids 159-169

Page 350 of 359

WC6008068 (Her//E/W/06206286 opc)

WO 02/08288 PCT/US01/21066

237/246

FIGURE 235

CCACCTGGCAGGAGCAGGACAGGACGGCCGGACGCCATGGCCGAGCTCCCGGGGCCCTT TCTCTGCGGGGCCCTGCTAGGCTTCCTGTGCCTGAGTGGCCTGGCCGTGGAGGTGAAGGTAC CCACAGAGCCGCTGAGCACGCCCCTGGGGAAGACAGCCGAGCTGACCTGCACCTACAGCACG TCGGTGGGAGACAGCTTCGCCCTGGAGTGGAGCTTTGTGCAGCCTGGGAAACCCATCTCTGA GTCCCATCCAATCCTGTACTTCACCAATGGCCATCTGTATCCAACTGGTTCTAAGTCAAAGC CACCCCTCAGATACTGGAACCTACCTCTGCCAAGTCAACAACCCACCAGATTTCTACACCAA TGGGTTGGGGCTAATCAACCTTACTGTGCTGGTTCCCCCCAGTAATCCCTTATGCAGTCAGA GTGGACAAACCTCTGTGGGAGGCTCTACTGCACTGAGATGCAGCTCTTCCGAGGGGGGCTCCT AAGCCAGTGTACAACTGGGTGCGTCTTGGAACTTTTCCTACACCTTCTCCTGGCAGCATGGT TCAAGATGAGGTGTCTGGCCAGCTCATTCTCACCAACCTCTCCCTGACCTCCTCGGGCACCT ACCGCTGTGTGGCCACCAACCAGATGGGCAGTGCATCCTGTGAGCTGACCCTCTCTGTGACC GAACCCTCCCAAGGCCGAGTGGCCGGAGCTCTGATTGGGGTGCTCCTGGGCGTGCTGTTGCT GTCAGTTGCTGCGTTCTGCCTGGTCAGGTTCCAGAAAGAGAGGGGGAAGAAGCCCAAGGAGA CATATGGGGGTAGTGACCTTCGGGAGGATGCCATCGCTCCTGGGATCTCTGAGCACACTTGT ATGAGGGCTGATTCTAGCAAGGGGTTCCTGGAAAGACCCTCGTCTGCCAGCACCGTGACGAC CACCAAGTCCAAGCTCCCTATGGTCGTGTGACTTCTCCCGATCCCTGAGGGCGGTGAGGGGG

Page 351 of 359

238/246

FIGURE 236

></usr/seqdb2/sst/DNA/Dnaseqs.min/ss.DNA108760

><subunit 1 of 1, 327 aa, 1 stop

><MW: 34348, pI: 7.88, NX(S/T): 2

MABLPOPFLOGALLGFLCLSCLAVEVKVPTEPLSTPLCKTAELICTYSTSVGDSFALEKS
FVQPKKPISESHPILYFTNGHLYPTGSKSKRVSLLQNPPTVGVATLKLTDVHPSDTGTYL
CQVNNPPDFYTNGLGLINLTVLVPPSNPLCSQSGGTSVGGSTALRCSSSEGAPKFVYNNV
RLGTFPTPSPGSMVQDEVSGQLILTNLSLTSSGTYRCVATNQMGSASCELTLSVTEPSQG
RVAGALIGVLLGVLLLSVAAFCLVRFQKERGKKPKETYGGSDLREDAIAPGISEHTCMRA
DSSKGFLERPSSASTVTTTKSKLPMV

Important features of the protein:

Signal peptide: Amino acids 1-20

WC0268268 (Her//E-/WO0Z06286 opc.)

Amino acius 1-2

Transmembrane domain:

Amino acids 242-260

N-glycosylation sites:

Amino acids 138-142;206-210

cAMP- and cGMP-dependent protein kinase phosphorylation site:

Amino acids 90-94

N-myristoylation sites:

Amino acids 11-17;117-123;159-165;213-219;224-230;244-250; 248-254

2.0

Amidation site:

Amino acids 270-274

Prokaryotic membrane lipoprotein lipid attachment site:

Amino acids 218-229

239/246

FIGURE 237

GGATGCAGCAGAGAGGAGCAGCTGGAAGCCGTGGCTCTCTTCCCTCTGCTGGGCG TCCTGTTCTTCCAGGGTGTTTATATCGTCTTTTCCTTGGAGATTCGTGCAGATGCCCATG TCCGAGGTTATGTTGGAGAAAAGATCAAGTTGAAATGCACTTTCAAGTCAACTTCAGATG TCACTGACAAGCTTACTATAGACTGGACATATCGCCCTCCCAGCAGCAGCACCACAGTAT CAATATTCATTATCAGTCTTTCCAGTACCCAACCACAGCAGCACATTTCGGGATCGGA TTTCCTGGGTTGGAAATGTATACAAAGGGGATGCATCTATAAGTATAAGCAACCCTACCA TAAAGGACAATGGGACATTCAGCTGTGCTGTGAAGAATCCCCCAGATGTGCACCATAATA TTCCCATGACAGAGCTAACAGTCACAGAAAGGGGTTTTGGCACCATGCTTTCCTCTGTGG CCCTTCTTTCCATCCTTGTCTTTTGTGCCCTCAGCCGTGGTGGTTGCTCTGCTGCTGGTGA GAATGGGCAGGAAGGCTGCTGGGCTGAAGAAGAGGAGCAGGTCTGGCTATAAGAAGTCAT CTATTGAGGTTTCCGATGACACTGATCAGGAGGAGGAGGAGGGCGTGTATGGCGAGGCTTT $\tt GTGTCCGTTGCGCTGAGTGCCTGGATTCAGACTATGAAGAGACATAT{\color{red}{\textbf{TGA}}} TGAAAGTCTG$ TATGACACAAGAA GAGTCACCTAAAGACAGGAAACATCCCATTCCACTGGCAGCTAAAGC CTGTCAGAGAAAGTGGAGCTGGCCTGGACCATAGCGATGGACAATCCTGGAGATCATCAG TAAAGACTTTAGGAACCACTTATTTATTGAATAAATGTTCTTGTTGTATTTATAAACTGT TCAGGAAGTCTCATAAGAGACTCATGACTTCCCCTTTCAATGAATTATGCTGTAATTGAA TGAAGAAATTCTTTTCCTGAGCA

Page 353 of 359

240/246

FIGURE 238

MQQRGAAGSRGCALFPLLGVLFFQGVYIVFSLEIRADAHVRGYVGEKIKLKCTFKSTSD VTDKLTIDWTYRPBSSSHTVSIFHYQSFQYPTTAGTFRDRIGWVGNYYKGDASISISNP TIKDNGTFSCAVKNPPDVHHNIPWTELTVTERGFGTMLSSVALLSILVFVPSAVVVALL LVRMGRKAAGLKKRSRSGYKKSSIEVSDDTDQBEBEAGMARLCVRCABCLDSDYBETT

Transmembrane domain

11-30 157-177

10, 1,,

WC0268268 (Mer//E-/W/06/206286 opc.)

N-glycosylation site 123-127

cAMP- and cGMP-dependent protein kinase phosphorylation site

189-193 197-201

Tyrosine kinase phosphorylation site

N-myristoylation site

5-11 8-14

124-130 153-159

Amidation site 181-185

Page 354 of 359

241/246

WO0268268 [Be://E-W/00206286 opc]

FIGURE 239

TCGTGTCTGCCGTCAACCGCAGGAGGATGAAGCTGCTGCTGGGCATCGCCTTGCTGGCCTACGTCGCCTCTGTT TGGGGCAACTTCGTTAATATGAGGTCTATCCAGGAAAATGGTGAACTAAAAATTGAAAGCAAGATTGAAGAAGAT GGTTGAACCACTAAGAGAAAATCAGAGATTTAGAAAAAAGCTTTACCCAGAAATACCCACCAGTAAAGTTTT TATCAGAAAAGGATCGGAAAAGAATTTTGATAACAGGAGGCGCAGGGTTCGTGGGCTCCCATCTAACTGACAAA $\tt CTCATGATGGACGCCACGAGGTGACCGTGGTGGACAATTTCTTCACGGGCAGGAAGAGAAACGTGGAGCACTG$ GATCGGACATGAGAACTTCGAGTTGATTAACCACGACGTGGTGGAGCCCCTCTACATCGAGGTTGACCAGATAT ACCATCTGGCATCTCCAGCCTCCCAAACTACATGTATAATCCTATCAAGACATTAAAGACCAATACGATT GGGACATTAAACATGTTGGGGCTGGCAAAACGAGTCGGTGCCCGTCTGCTCCTGGCCTCCACATCGGAGGTGTA TGGAGATCCTGAAGTCCACCCTCAAAGTGAGGATTACTGGGGCCACGTGAATCCAATAGGACCTCGGGCCTGCT ACGATGAAGGCAAACGTGTTGCAGAGACCATGTGCTATGCCTACATGAAGCAGGAAGGCGTGGAAGTGCGAGTG GCCAGAATCTTCAACACCTTTGGGCCACGCATGCACATGAACGATGGGCGAGTAGTCAGCAACTTCATCCTGCA GGCGCTCCAGGGGGAGCCACTCACGGTATACGGATCCGGGTCTCAGACAAGGGCGTTCCAGTACGTCAGCGATC TAGTGAATGGCCTCGTGGCTCTCATGAACAGCAACGTCAGCAGCCCGGTCAACCTGGGGAACCCAGAAGAACAC ACAATCCTAGAATTTGCTCAGTTAATTAAAAACCTTGTTGGTAGCGGAAGTGAAATTCAGTTTCTCTCCGAAGC CCAGGATGACCCACAGAAAGAAAACCAGACATCAAAAAAGCAAAGCTGATGCTGGGGTGGGAGCCCGTGGTCC CGCTGGAGGAAGGTTTAAACAAAGCAATTCACTACTTCCGTAAAGAACTCGAGTACCAGGCAAATAATCAGTAC TCAAAAACTGCAGATTTTGCCTTGCACTTTTTGAATCTCTCTTTTTATGTAAAATAGCGTAGATGCATCTCTG AAATGAGTCGTTATACTATGCATAAAGAAAAATCCTAGCAGTATTGTCAGGTGGTGGTGCGCCGGCATTGATTT TAGGGCAGATAAAAGAATTCTGTGTGAGAGCTTTATGTTTCTCTTTTAATTCAGAGTTTTTCCAAGGTCTACTT TTGAGTTGCAAACTTGACTTTGAAATATTCCTGTTGGTCATGATCAAGGATATTTGAAATCACTACTGTGTTTT GCTGCGTATCTGGGGCGGGGCAGGTTGGGGGGCACAAAGTTAACATATTCTTGGTTAACCATGGTTAAATATG CTATTTTAATAAAATATTGAAACTCA

WO 02/08288

WO0268268 [Be://E-W/00206286 opc]

PCT/US01/21066

Page 355 of 359

242/246

FIGURE 240

MVSKALLRLVSAVNRRRKLLLGTALLAYVASVWGNFVMRRSIQENGELKIESKIEEMVEPL REKIRDLESFTÖKYEPVKFISEKDRKRILITGGGGFVGSHLTDKLMMDGGEVYVVONFFTG RKRVEHWIGHENFELINHDVVEPLYIEVDQIYHLASPASPPNYMYNPIKTLKTNTIGTINM LGLAKRVGARLLLASTSEVYGDFEVHPQSEDDWGHTNFIGFRACYDEGKVVAETMCYAYNKQ EGVEVRVARIFNTFOFRHHMNDGRVVSNFILQALQGEPLTVYGSGSQTRAFQYYSDLVNGLV ALMNSNVSSPVNLGNFEEHTILEFAQLIKKLVGSGSEIQFLSEAQDDPQKRKPDIKKAKLML GWEPVVPLEEGLNKAIHYRKELEYQANNQYIEVRPARIKKGRTRHS

Important features: Signal peptide: amino acids 1-32

N-glycosylation site: amino acids 316-320

Tyrosine kinase phosphorylation site: amino acids 235-244

N-myristoylation sites: amino acids 35-41,101-107,383-389

Amidation sites: amino acids 123-127,233-237

Page 356 of 359

WC6008068 (Her//E/W/06206286 opc)

WO 02/08288 PCT/US01/21066

243/246

FIGURE 241

GCCCGGTGGAGAATTAGGTGCTGCTGGGAGCTCCTGCCTCCCACAGGATTCCAGCTGCAGGG AGCCTCAGGGACTCTGGGCCGCACGGAGTTGGGGGCATTCCCCAGAGAGCGTCGCCATGGTC TGCAGGGAGCAGTTATCAAAGAATCAGGTCAAGTGGGTGTTTGCCGGCATTACCTGTGTGTC TGTGGTGGTCATTGCCGCAATAGTCCTTGCCATCACCCTGCGGCGGCCAGGCTGTGAGCTGG AGGCCTGCAGCCCTGATGCCGACATGCTGGACTACCTGCTGAGCCTGGGCCAGATCAGCCGG CGAGATGCCTTGGAGGTCACCTGGTACCACGCAGCCAACAGCAAGAAAGCCATGACAGCTGC CCTGAACAGCAACATCACAGTCCTGGAGGCTGACGTCAATGTAGAAGGGCTCGGCACAGCCA CAGTGGCTGGACGCTGTGCTGGGCTCTTCCCAAAAGGGCATCAAACTGGACTTCAAGAACAT CAAGGCAGTGGGCCCCTCCCTGGACCTCCTGCGGCAGCTGACAGAGGAAGGCAAAGTCCGGC GGCCCATATGGATCAACGCTGACATCTTAAAGGGCCCCAACATGCTCATCTCAACTGAGGTC AATGCCACACAGTTCCTGGCCCTGGTCCAGGAGAAGTATCCCAAGGCTACCCTATCTCCAGG CTGGACCACCTTCTACATGTCCACGTCCCCAAACAGGACGTACACCCAAGCCATGGTGGAGA AGATGCACGAGCTGGTGGGAGGAGTGCCCCAGAGGGTCACCTTCCCTGTACGGTCTTCCATG GTGCGGGCTGCCTGGCCCCACTTCAGCTGGCTGCTGAGCCAATCTGAGAGGTACAGCCTGAC GCTGTGGCAGGCTGCCTCGGACCCCATGTCGGTGGAAGATCTGCTCTACGTCCGGGATAACA CTGCTGTCCACCAAGTCTACTATGACATCTTTGAGCCTCTCCTGTCACAGTTCAAGCAGCTG GCCTTGAATGCCACACGGAAACCAATGTACTACACGGGAGGCAGCCTGATCCCTCTTCTCCA GCTGCCTGGGGATGACGGTCTGAATGTGGAGTGGCTGGTTCCTGACGTCCAGGGCAGCGGTA AAACAGCAACAATGACCCTCCCAGACACAGAAGGCATGATCCTGCTGAACACTGGCCTCGAG GGAACTGTGGCTGAAAACCCCGTGCCCATTGTTCATACTCCAAGTGGCAACATCCTGACGCT GGAGTCCTGCCTGCAGCAGCTGGCCACACATCCCGGACACTGGGGCATCCATTTGCAAATAG TGGAGCCCGCAGCCTCCGGCCATCCCTGGCCTTGCTGGCACGCCTCTCCAGCCTTGGCCTC TTGCATTGGCCTGTGTGGGTTGGGGCCAAAATCTCCCACGGGAGTTTTTCGGTCCCCGGCCA TGTGGCTGGCAGAGAGCTGCTTACAGCTGTGGCTGAGGTCTTCCCCCACGTGACTGTGGCAC CAGGCTGGCCTGAGGAGGTGCTGGGCAGTGGCTACAGGGAACAGCTGCTCACAGATATGCTA GAGTTGTGCCAGGGGCTCTGGCAACCTGTGTCCTTCCAGATGCAGGCCATGCTGCTGGGCCA CAGCACAGCTGGAGCCATAGGCAGGCTGCTGGCATCCTCCCCCGGGCCACCGTCACAGTGGAG CACAACCCAGCTGGGGGCGACTATGCCTCTGTGAGGACAGCATTGCTGGCAGCTAGGGCTGT GGACAGGACCCGAGTCTACTACAGGCTACCCCAGGGCTACCACAAGGACTTGCTGGCTCATG TTGGTAGAAACTGAGCACCCAGGGGTGGTGGGCCAGCGGACCTCAGGGCGGAGGCTTCCCAC

Page 357 of 359

PCT/US01/21066

244/246

FIGURE 242

></usr/segdb2/sst/DNA/Dnasegs.min/ss.DNA119514

><subunit 1 of 1, 585 aa, 1 stop

><MW: 64056, pI: 6.58, NX(S/T): 5

MVCREQLSKNQVKWVFAGITCVSVVVIAAIVLAITLRRPGCELEACSPDADMLDYLLSLG QISRRDALEVTWYHAANSKKAMTAALNSNITVLEADVNVEGLGTANETGVPIMAHPPTIY SDNTLEQWLDAVLGSSQKGIKLDFKNIKAVGPSLDLLRQLTEEGKVRRPIWINADILKGP NMLISTEVNATOFLALVOEKYPKATLSPGWTTFYMSTSPNRTYTOAMVEKMHELVGGVPO RVTFPVRSSMVRAAWPHFSWLLSOSERYSLTLWOAASDPMSVEDLLYVRDNTAVHOVYYD IFEPLLSQFKQLALNATRKPMYYTGGSLIPLLQLPGDDGLNVEWLVPDVQGSGKTATMTL PDTEGMILLNTGLEGTVAENPVPIVHTPSGNILTLESCLQQLATHPGHWGIHLQIVEPAA LRPSLALLARLSSLGLLHWPVWVGAKISHGSFSVPGHVAGRELLTAVAEVFPHVTVAPGW PEEVLGSGYREOLLTDMLELCOGLWOPVSFOMOAMLLGHSTAGAIGRLLASSPRATVTVE HNPAGGDYASVRTALLAARAVDRTRVYYRLPOGYHKDLLAHVGRN

Important features of the protein:

Transmembrane domain:

WCG268268 [IB#7/E-AV-06206236 opc.]

WO 02/08288

Amino acids 18-37 (Possible type II)

N-glycosylation sites:

Amino acids 89-93:106-110:189-193:220-224:315-319

Tyrosine kinase phosphorylation site:

Amino acids 65-74

N-myristovlation sites:

Amino acids 101-107;351-357;372-378;390-396;444-450;545-551

Aminotransferases class-V pyridoxal-phosphate attachment site:

Amino acids 312-330

Page 358 of 359

WC0268268 [Be://E-W/00206286 opc]

245/246

FIGURE 243

CTTCAGAACAGGTTCTCCTTCCCCAGTCACCAGTTGCTCGAGTTAGAATTGTCTGCAATGCC CGCCTGCAGAAATCTGTGAGCTCTTTCCTTATGGGGACCCTGGCCACCAGCTGCCTCCTTC TCTTGGCCCTCTTGGTACAGGGAGGAGCAGCTGCGCCCATCAGCTCCCACTGCAGGCTTGAC AAGTCCAACTTCCAGCAGCCCTATATCACCAACCGCACCTTCATGCTGGCTAAGGAGGCTAG CTTGGCTGATAACAACACAGACGTTCGTCTCATTGGGGAGAAACTGTTCCACGGAGTCAGTA TGAGTGAGCGCTGCTATCTGATGAAGCAGGTGCTGAACTTCACCCTTGAAGAAGTGCTGTTC CCTCAATCTGATAGGTTCCAGCCTTATATGCAGGAGGTGGTGCCCTTCCTGGCCAGGCTCAG CAACAGGCTAAGCACATGTCATATTGAAGGTGATGACCTGCATATCCAGAGGAATGTGCAAA AGCTGAAGGACACAGTGAAAAAGCTTGGAGAGAGTGGAGAGATCAAAGCAATTGGAGAACTG GATTTGCTGTTTATGTCTCTGAGAAATGCCTGCATTTGACCAGAGCAAAGCTGAAAAATGAA CAAAAGGAAGATGGGAAGCCAAACTCCATCATGATGGGTTGGATTCCAAATGAACCCCTGCGT TAGTTACAAAGGAAACCAATGCCACTTTTGTTTATAAGACCAGAAGGTAGACTTTCTAAGCA TTTAAATAATTGTCTTTTTCCATAAAAAAGATTACTTTCCATTCCTTTAGGGGAAAAAACCC TAAGACTGCATTTTATTATATCATTTTATTAATATGGATTTATTATATAGAAACATCATTCG ATATTGCTACTTGAGTGTAAGGCTAATATTGATATTTATGACAATAATTATAGAGCTATAAC ATGTTTATTTGACCTCAATAAACACTTGGATATCCC

Page 359 of 359

246/246

FIGURE 244

MAALOKSVSSFIMGTLATSCILLLAILVQGGAAAPISSHCRIDKSNFQQPYITNRTFMLAKE ASLADNNTDVRLIGEKLFHGVSMSERCYLMKQVLNFTLEEVLFPQSDRFQPYMGEVVPFLAR LSNRLSTCHIRGDDLHIQRNVQKLKDTVKKLGESGBIKAIGELDLLFMSLRNACI

Important features of the protein: Signal peptide:

amino acids 1-33

WCG268268 [Re://E/W/06266286 opc]

N-glycosylation sites. amino acids 54-58, 68-72, 97-101

N-myristoylation sites. amino acids 14-20, 82-88

Prokaryotic membrane lipoprotein lipid attachment site. amino acids 10-21